AD-A247 159

TATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	12/91	FINAL 8 Sept 88 - 7 Sept 91

4. TITLE AND SUBTITLE
The Coordinated Noninvasive Studies (CNS) Project. 2 vols: Text, and Appendices

5. FUNDING NUMBERS
G AFOSR 88-0352
61102F
PR- 2313
TA- A6

6. AUTHOR(S)
Judith L.Lauter, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Arizona
Tucson AZ 85721

8. PERFORMING ORGANIZATION REPORT NUMBER
AFOSR-TR- 92 0146

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
AFOSR
Life Sciences Directorate
Bolling AFB
Washington DC 20332

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release;
Distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

The CNS Project combines several noninvasive methods for monitoring brain structure and function in a test battery. Phase One (1988-1991) focussed on neuroanatomical and neurophysiological correlates of behavioral "ear advantages" for two sets of complex sounds. Fifteen subjects neurologically normal according to conventional standards were tested with dichotic listening (2 measures), MRI (2 measures), evoked potentials (2 measures), and qEEG (4 measures). One subject was also tested under similar conditions with PET. Results indicated: 1) Each individual had a distinct "sidedness bias" articulated in terms of a combination of anatomical and physiological variables, 2) These individual patterns cut across conventional categories such as gender and handedness, 3) In some of the subjects, these "CNS profiles" comprised "internally consistent" patterns of asymmetries linking subcortical physiology, cortical anatomy and cortical physiology, 4) In others, departures from such consistency signalled evidence of a variety of subtle neuropathologies, such as stuttering, mild learning disorder, central auditory dysfunction, or a history of hyperactivity and/or substance abuse.

14. SUBJECT TERMS
brain imaging, human neuroscience, brain asymmetries, evoked potentials, qEEG, MRI, PET

15. NUMBER OF PAGES
193

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
(U)	(U)	(U)	(U)

The Coordinated Noninvasive Studies (CNS) Project

Phase One

Judith L. Lauter, Ph.D.

AFOSR 88-0352
University of Arizona
1988-1991

FINAL REPORT
December 1991

The Coordinated Noninvasive Studies (CNS) Project, Phase One: 1988 - 1991. FINAL REPORT.

Outline

I. Introduction and Proposed Goals.

Although sensory-central-nervous-system anatomy and physiology have been studied in non-human animals at a number of levels of detail, from cell-membrane physiology to pathway topography, students of sensory processing in humans have had a very few, limited sources of data: 1) psychophysical documentation of the "whole-organism response," 2) gross physiological measures such as strip-chart EEG, and 3) studies of brain pathology. The information regarding the organization of human sensory systems available from these sources is highly restricted, in no way approaching the discreteness of data available for non-human brains. Thus, although an array of highly sophisticated psychophysical descriptions of human perceptual capabilities has been formulated, next to nothing is known regarding the central nervous system mechanisms underlying behaviorally-observed human sensory performance.

Over the last decade, a number of noninvasive methods for studying brain anatomy and physiology have become available. Some have sprung from research in physics or chemistry (e.g., Magnetoencephalography MEG, Magnetic Resonance Imaging MRI, Magnetic Resonance Spectroscopy MRS), and others represent the latest stage in technologies designed to study biological systems, often emerging as the result of an increasingly sophisticated use of computers for data collection and analysis (quantitative electroencephalography qEEG, Positron Emission Tomography PET).

The Coordinated Noninvasive Studies (CNS) Project was designed to bring together several of these noninvasive methods (including behavioral techniques) in a test-battery approach for studying human brains, with the initial focus on perceptual asymmetries. Thus the acronym for the Project describes both the topic (the human CNS) as well as the method, an experimental design which coordinates the unique capabilities and dependent variables characteristic of a variety of noninvasive methods to the end of studying neuroanatomical and neurophysiological correlates of human behavior.

While brain functional asymmetries represent one of the oldest principles of nervous-system organization, they have not received the serious attention they deserve, being limited largely to invocations in "pop" neuropsychology to explain a range of phenomena, from recovery from aphasia to distinctions between types of IQ. Ideas of asymmetry in humans have been closely linked with observations regarding language behavior, and thus a more general perspective on their adaptive function in the evolution of vertebrates has generally been lacking, and conceptions that may lead to a "unified theory" of functional asymmetries are still only in their infancy.

However, a developmental line in the expression of functional asymmetries may be traced which serves to illuminate the assumptions on which the approach of the CNS Project depends. Specialization across the midline is one of the oldest principles of nervous-system organization. Although members of the phylum Chordata are characterized as being "bilaterally symmetrical," asymmetrical principles of organization play a clear role even in invertebrates, where the right side of the nervous system is specialized for motor control of the right side of the body, and vice versa. This can be described as an asymmetry based on side-of-space, with an ipsilateral emphasis. This specialization based on side of space may be interpreted as a means to the end of complementary coordination of the two CNS/body halves, so that, e.g., rhythmic movements such as walking are possible.

In vertebrates, an evolutionary "twist" along the long axis of the body, continues this principle, with specialization of each side of the nervous system based on such "first level" side-of-space distinctions in motor control, only now with a contralateral emphasis. There are, in addition, sensory analogues to this plan, whereby stimuli occurring in the left half of space (whether the left-side somatosensory surface, the left ear's sound field, or the left visual half field) are processed most directly by appropriate nuclei on the right side of the central nervous system, and vice versa.

It is possible that this principle of specialization across a central (i.e., CNS) midline to achieve the goal of coordinated behavior across a peripheral midline (i.e., two ears, two visual half fields, left vs. right side of the body) may have been elaborated into a second-level expression of lateralization, namely, specialization based on physical characteristics of sensory or motor phenomena. Thus, as discussed by Lauter (1983) for auditory and Sergent (1983) for visual phenomena, traditional descriptions of lateralization in humans in terms of "speech" vs. "music," or "letters" vs. "nonsense patterns" can often be more parsimoniously accounted for in dimensional terms, e.g., fast vs. slow auditory rates, high vs. low visual frequencies. Additionally, one may posit that the principles of this physical division of the world in and around an organism are consistent across modalities, based on analogous characteristics, e.g., fast auditory rates, high visual frequencies, closely-spaced tactile patterns, small-angle motor gestures.

Thus we may predict that in any given testing condition involving presentation of controlled stimuli, the performance of a subject may reveal functional asymmetries that represent the influence of two factors: 1) the "contralateral effect," based on the side-of-space source of asymmetries, where processing on that side of the CNS opposite the side of input is favored, and 2) an effect based

on the physical characteristics source of asymmetries, where processing on that side of the CNS specialized for those stimulus characteristics on which successful task completion depends will be favored. Determining the degree to which asymmetries organized according to side of space differ from those based on physical characteristics of phenomena--whether of auditory, visual, or somatosensory patterns or of motor gestures, and the ways in which they interact in different types of performance--is thus basic to an evolutionary perspective on brain lateralization.

There may be a third and evolutionarily more advanced level of expression of this same principle, involving more abstract mental operations such as semantic comprehension of a sentence or performance of mental arithmetic. However, a sophisticated understanding of any higher-level principle of lateralization must depend on a more complete understanding of how lower-level principles such as side of space and physical stimulus characteristics are expressed in brain specializations, as well as an appreciation of the degree of difference and similarity among individuals in the details of these expressions.

Finally, the action of all of these principles of asymmetrical organization expressed during "exogenous" tasks demands may be overlaid upon individual patterns of organization which involve an endogenous "sidedness bias" favoring one side or the other. Such biases have been observed in humans and in other animals, and must arise first of all from the basic impossibility of building a body and/or brain which is truly "bilaterally symmetrical." However, little is known about individual variations in the nature of such biases, and whether the direction and magnitude of sidedness bias are determined by random variation, or by genetic influences, has yet to be determined. It may be virtually impossible to interpret observations of asymmetries related to such factors as side of space, physical characteristics of stimuli, and cognitive task components, in the absence of information characterizing each individual in terms of sidedness biases.

Thus interactions among the four types of asymmetries are to be expected. Responses studied in terms of side of space must be calibrated to the underlying sidedness bias subject-by-subject. Behavioral techniques used to study perceptual asymmetries, such as dichotic listening, and visual half-field presentation, must be designed to measure perceptual asymmetries due to physical characteristics to the extent that these exist over and above sidedness bias as well as side-of-space asymmetries -- since in these experiments, contralateral effects are available on every trial. At the same time, studies of perceptual asymmetries must control for differences in cognitive task, to ensure that observed differences will be due to stimulus class alone. Thus for identifying the mechanisms underlying behaviorally-observed asymmetries, it may be crucial to remember that asymmetries in CNS stimulus processing depend on all four factors, and that one

should in every case attempt to identify their separate contributions to observed asymmetries in individual performance.

The measurement techniques to be described below are ideally suited for this purpose. Many of the measures provide a view of the system "at rest," for quantification of sidedness bias. With each physiological test, it is possible to use the subject as her/his own control, for presentation of stimuli under a number of conditions designed to help parse out the contributions of the different sources of asymmetries to the total response. In addition, several of the physiological techniques provide the opportunity to measure brain responses under test conditions mimicking those used in the behavioral laboratory, such that one can examine the degree of match between each of the details of the behavioral testing on the one hand, and results observed during brain monitoring on the other.

Finally, the test-battery approach represented by the CNS Project should be the optimal solution for studying aspects of behavior such as functional asymmetries. By "coordinating" the noninvasive methods, via a repeated-measures design where each subject is tested on all devices under a variety of test conditions, the series of experiments should provide an overall view of the brain based on graded distinctions in spatial and temporal resolution. This is illustrated in Figs. i-1 and i-2.

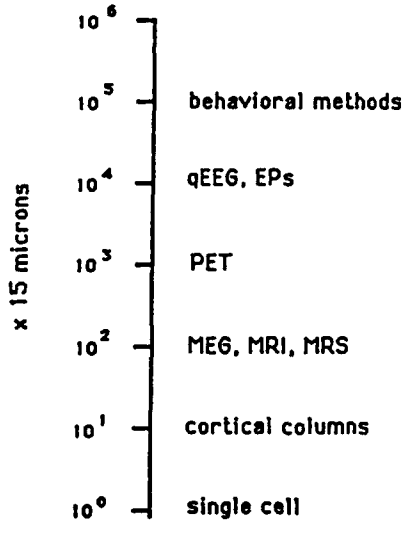


Figure i-1: Spatial resolution scale for six levels. This figure illustrates the fact that in terms of spatial resolution, the devices to be included in the CNS Project span a range linking the "whole organism" response sampled in behavioral testing (most coarse resolution) with the level of resolution available with microelectrodes, used to study macrounits of brain organization such as cortical columns, and microunits such as single neurons.

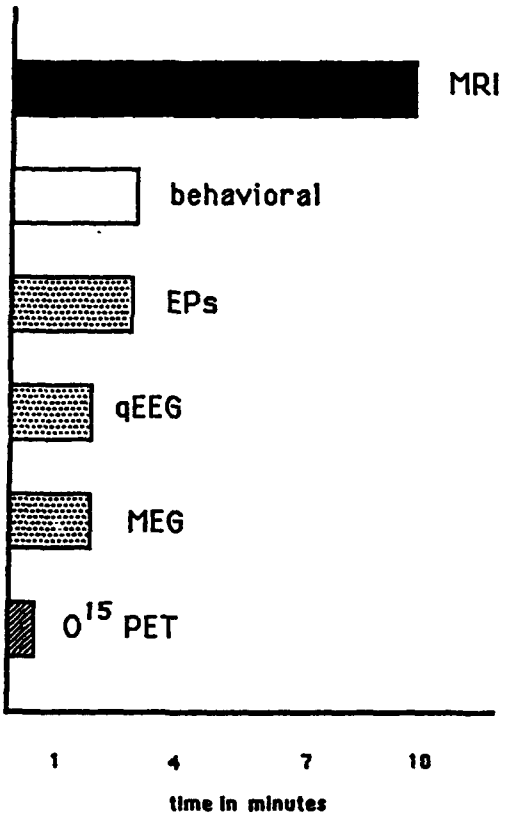


Figure i-2: Temporal resolution scale comparing six approaches. Here the devices are contrasted in terms of temporal resolution, a smaller range (than spatial), of two-fold instead of ten-fold steps, from 1 minute to 2 hours. Note that the ranking of devices is different for the two types of resolution scale.

The two graphs together suggest that there are trade-offs in these two types of resolution that make some devices more useful than others. For example, although magnetic resonance spectroscopy offers excellent spatial resolution (approximately 1 mm), the time required for data collection (10-20 minutes) is daunting from the point of view of neurophysiological applications. On the other hand, although the PET scan is an order of magnitude more coarse in terms of spatial resolution (5-15 mm), its temporal resolution (using oxygen-15, 40 sec) makes it very attractive for studies of normal brain function.

Prior to the type of extensive testing proposed here, there has been no way to judge which device, if used singly, would provide the most informative results

for students of normal human brain function. The view of the brain collected with "poor" temporal resolution (e.g., MRI/MRS) may in fact be more appropriate for comparisons with behavioral results that are collected over a similar time scale. Similarly, results collected in "coarse" spatial resolution (e.g., PET's 5-15 mm) may reflect a level of brain organization that is more relevant to understanding behavior than the "microneurophysiology" provided by microelectrodes. Thus the hope of this research is twofold: 1) it should provide insights regarding auditory processing in particular and functional asymmetries in general, and 2) it will serve to demonstrate the revolutionary potential of new noninvasive methods for studying the mechanisms underlying human behavior.

Functional neurophysiology, and in particular the study of sensory processing, has over the last 40 years been dominated by microelectrode technology, and its associated constraints on the types of subjects (both topics and organisms) that can be studied. It is only recently that noninvasive methods for studying human brain anatomy and physiology provide the technology for a "new sensory psychology," and have already ushered in--virtually unnoticed--the era of "human neuroscience."

Specific hypotheses. The first hypothesis of the CNS Project is that within each individual, measures of neuroanatomical and neurophysiological asymmetries will reveal patterns of auditory CNS design that are "internally consistent." For example, if an individual system has an underlying bias toward one side or the other, this bias should normally be expressed consistently across the measures studied -- e.g., a system that favors the right ear peripherally should favor the left side of the system centrally (where "favor" is a term to be quantitatively defined via the various dependent variables).

The second hypothesis is that these underlying patterns of asymmetrical organization should be systematically related to behavioral asymmetries such as those measured in terms of EAs. Thus, as described below, patterns of "relative ear advantages" (RelEAs) may be used to formulate detailed hypotheses for each subject, which will be "tested" by means of the other measures in the battery: e.g., does a "split" RelEA pattern reflect a system which has no sidedness bias, in which syllables are processed primarily in the left hemisphere, and tone patterns processed primarily in the right, or is it an external sign of a particular style of internal organization?

II. Test battery: methods and results

A. SUBJECTS

The original proposal called for testing a total of eight subjects on a battery of six tests (dichotic listening, MRI, EPs, qEEG, MEG, and PET). Truncation of funding during the period of support made it impossible to meet the travel and fee-for-service expenses involved in the out-of-state MEG and PET testing. Thus plans were revised such that more subjects were tested via the four on-site methods, for a total of 15 individuals tested on the first four tests named above. Twelve of these were selected to be audiologically normal by test, and neurologically normal by report, with no history of speech, language, or hearing disorder. An additional three subjects were recruited to provide instances of disorders hypothetically expressed in the measures of asymmetry under study: one individual reporting a history of stuttering, and two who had been previously diagnosed as having a "central auditory processing disorder."

Other individual characteristics are noted in Table I, where data for the subjects are arranged in ascending order by age; the three "patients" are underlined. Two of the normals and two of the patients were males; the rest were females; ages ranged from 16 to 45. Sidedness was described but not controlled; sidedness configurations are indicated in Table I. All except JL (the PI) were paid for their participation.

Table I. CNS Project subjects

Initials	Gender	Age	personal sidedness	family sidedness*	twins*
MG	M	16	R	Lf	mYfN
EE	F	17	R	R	mNfY
WB	F	20	L	Lf	mYfY
AB	F	22	R	R	mNfN
HR	F	22	R	Lb	mYfY
PR	M	23	R	R	mNfN
MAB	M	27	R	Lf	mNfN
JS	M	29	L	Lb	mNfN
CJS	F	33	R	Lf	mNfY
JLM	F	38	R	R	mNfN
SHB	F	40	R	R	mNfN
CB	F	43	R	Lf	mNfN
ES	F	45	R	Lf	mYfN
JL	F	45	R	R	mYfN
SJ	F	45	L	Lm	mYfN

* m = mother, f = father, b = both

B. BEHAVIORAL TESTING

Methods. Two sound sets were used for dichotic testing. The first was a set of synthetic stop-CV syllables (bdgptk + a), included in our previous experiments (Lauter 1982, 1983, 1984). The second set consisted of the six orders of three pure tones (1400, 1480, 1560 Hz), with each sequence of three timed with 200 msec between onsets, similar to tone patterns tested in previous work (Lauter, op cit.)

Facilities in the two Psychoacoustic Laboratories at the University of Arizona (funded by AFOSR 85-0379) were used for preparing the stimuli and testing the subjects. Each site was equipped with an AT&T 6300 microcomputer fitted with a Data Translation DT2801A board, with appropriate peripherals. Subject stations were located in sound-treated rooms, and included a computer monitor for presentation of temporal cues and feedback, a keyboard for recording responses, and a pair of AKG K141 stereo earphones.

The software package SONOS developed for those laboratories (funding by AFOSR 85-0379) was used to: 1) record the synthetic syllables onto hard disk; 2) generate and edit the tone sequences; 3) group the syllables and tone sequences into sets for experimental presentation; 4) select timing and ear-of-presentation conditions; 5) execute experimental blocks, including timing, stimulus presentation, feedback display, and response collection; and 6) record trial-by-trial data in terms of stimulus per channel, and response.

Test procedures were similar to those used in our earlier experiments (Lauter, op cit.). Subjects were introduced to the sounds sets via monaural listening without required responses, then were tested with monaural presentation, with ear-of-presentation alternating from 36-trial block to block. When performance reached ceiling performance in both ears, dichotic testing began. Dichotic sessions started with two monaural test blocks, one to each ear, and continued with six dichotic blocks. The initial ear-of-report in each session was assigned as shown in the schedule shown below; these assignments were designed both to allow the advantage of practice to accrue to the hypothetically nonpreferred ear for each sound, and to counterbalance ear-of-report orders.

Guidelines from our previous work regarding level of performance were followed to ensure that ear advantages were collected as far as possible under "equal intelligibility" conditions. That is, dichotic testing for the syllables continued until a mid-range level of performance (between approximately 30 and 80 p(c)) was achieved in at least one ear (either ceiling or floor scores were acceptable in the other ear). For the tone patterns, a series of "graduated difficulty" versions were available to assist in achieving this goal; the versions were identical in every way save the size of the frequency step, ranging from a

whole-tone down to a quarter-tone step.

In the dichotic portion of each session, ear-of-report was alternated from block to block until three blocks of right-ear report and three of left-ear report were collected for that session. Scores were recorded in terms of percent correct on each block. At the end of two such dichotic sessions at the appropriate performance level (total of 216 trials per ear of report) for a sound set, an overall left-ear score and right-ear score was calculated, and the two values subtracted to yield an EA for that subject for that sound.

The behavioral test schedule was as follows:

WEEK ONE

Session	1	syllables	block 1 = R-ear report
	2	syllables	L
	3	200-msec tones	L
	4	200-msec tones	R

WEEK TWO

Session	1	200-msec tones	R
	2	200-msec tones	L
	3	syllables	L
	4	syllables	R

WEEK THREE (repeat of week two)

WEEK FOUR (repeat of week one)

Methods note. For the majority of the subjects, behavioral testing methods were as given above. However, during the period of AFOSR 88-0352, funding from another source supported work on design and development of Macintosh-based dichotic-listening testing software (Central Auditory Diagnostics for the Macintosh, MacCAD: see Appendix E for details). As a result, ear advantages for some of the CNS Project subjects were collected using MacCAD equipment and procedures. These included: a Macintosh II or SE/30 fitted with AKG K141 stereo earphones, and the MacCAD software, a Hypercard-based program which incorporates many of the dichotic-listening procedures noted above.

The primary departures contrasting MacCAD with those PC-based methods are accounted for by features designed to streamline testing for both normals and patients, while retaining the procedural integrity of methods for collecting reliable ear advantages. Changes include: 1) sound sets represented by three alternatives rather than six; 2) both sound sets tested in a single test session, with

ear advantages for each based on a total of 36 trials per ear of report per sound; and 3) graduated difficulty versions for both synthetic syllables and tone patterns. Observations of test results in the same subject using both methods indicate that the two approaches yield comparable results.

Results. Individual data in terms of average percent-correct scores per sound set per ear of report, and resulting ear advantages calculated as percent-difference scores, are presented in Table II, arranged in ascending order by age. Scheduling constraints precluded collecting tone-pattern EAs in three subjects (HR, JLM, and PR). Note the individual differences in EA shown for each sound set: dichotic syllables evoke EAs ranging from 29 LEA (MAB) to 60 REA (SHB) while EAs for the tone patterns ranged from 35 LEA (SHB) to 22 REA (SJ).

Relative-EA (RelEA) patterns were plotted for each subject (Fig. B1), arranged according to type of pattern (whether "split," 2 LEAs, or 2 REAs). Note that in spite of the individual differences in terms of "absolute EA" for each sound set described above, there is an obvious basis for consensus among these subjects in terms of the RelEA pattern configuration: in all but three instances (indicated as a "/reversed" pattern), syllables evoke an EA that is to-the-right of the EA score for the tone patterns. As described in our earlier dichotic-listening reports (Lauter, op cit.), this is true in spite of individual differences in type of pattern, whether the EAs are split between LEA and REA, whether they are both LEAs or are both REAs.

Reference to the individual data presented in Table I suggests no obvious match between these individual characteristics and RelEA pattern type: in fact, there are no significant overall correlations between age, personal handedness, family handedness, and type of RelEA pattern (r for all comparisons < .44). However, it may be important that, similar to previous observations (Lauter, op cit.), all three cases of "reversed" EAs occur in individuals who are from left-handed families.

Table II. Dichotic listening results

Initials	syllables			tone patterns		
	R	L	EA*	R	L	EA*
MG	48	51	L3	58	49	R8
EE	76	47	R24	60	77	L12
WB	66	30	R38	42	53	L12
AB	60	70	L8	68	89	L13
HR	80	53	R20	-	-	-
PR	75	50	R20	-	-	-
MAB	31	56	L29	73	69	R3
JS	47	58	L10	52	76	L19
CJS	61	41	R20	49	63	L13
JLM	53	45	R8	-	-	-
SHB	89	22	R60	47	97	L35
CB	62	75	L9	54	80	L19
ES	56	47	R9	73	72	R1
JL	79	60	R14	58	77	L14
SJ	80	68	R8	83	53	R22

*EA calculated as percent difference = [(L-R)/(L+R)]100

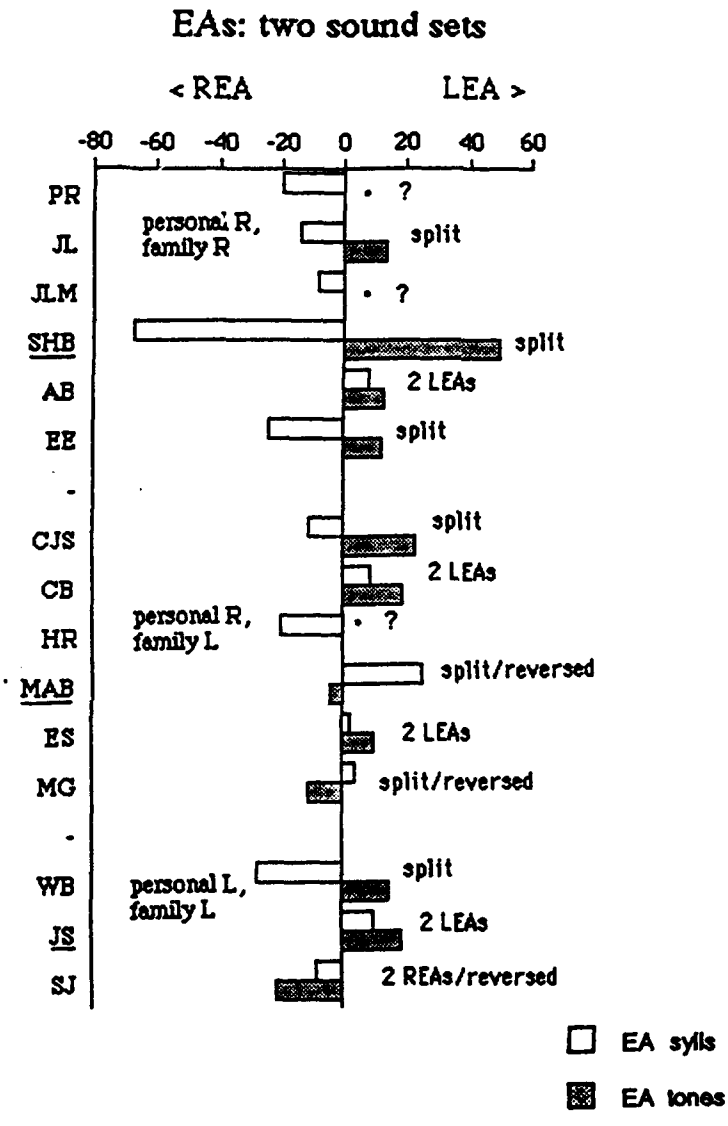


Figure B1. Ear advantages (EAs) for 15 subjects tested on a set of synthetic stop-consonant-vowel nonsense syllables, and a set of three-tone patterns with 200 ms between tone onsets. In spite of the individual differences in the "absolute ear advantage" for any one sound set, there is a clear consensus among individuals in terms of "relative ear advantages" for the two sets. Specifically, the syllables evoke an EA that is "to the left" of the EA for the tones in all but three of these subjects; the three with a "reversed" relative EA pattern are from left-sided families.

C. Magnetic Resonance Imaging (MRI)

Methods. Procedures for data collection and analysis were identical to those developed by Plante (Plante 1991, Plante & Turkstra 1991, Plante et al 1989, 1991), which are derived from earlier work on anatomical asymmetries in human brains studied via autopsy dissection and CT (see Plante et al 1989 for references). The collaboration of E. Plante in assisting with scheduling, testing, and analyzing for the MRI portion of this experiment is gratefully acknowledged.

MRI images were generated using a Toshiba 0.5 Tesla system, at the MRI Facility of the University of Arizona Medical Center, on a fee-for-service basis at a rate of $300 per subject. Coronal and axial (horizontal) planes were sampled with contiguous slices through the full volume of the cerebrum, and the sagittal plane was sampled with noncontiguous (2.5 mm gap) slices. Slice thickness for all planes was 5 mm. Axial planes were placed on the canthal-meatal line to ensure head orientation appropriate for measuring asymmetries related to peri-Sylvian areas, and to control degree of head tilt across subjects. A TR (magnetization) time of 2800 msec was used, with TE (decay-sampling) times of 20 msec and 80 msec; the TE values were chosen to ensure clear distinctions between grey and white matter--an early sampling time where CSF shows as dark, making sulcal margins easy to identify, and gray matter shows as lighter, and a later sampling time for complementary images, where gray matter shows as darker.

Subject preparation was minimal, consisting only of ensuring that the subject was comfortable, with the head firmly fixed within the headholder with its foam inserts. During scanning, subjects lay quietly, with eyes closed or open, and were instructed to remain as still as possible for the duration of the scan. A total of approximately one hour was required to obtain scans at the indicated resolutions in all three planes.

Data analysis made use of image films obtained from the MRI Center, and was accomplished on a PC-based video analysis system running Jandel's Java image-processing software. A number of measures of asymmetries similar to those reported previously for autopsy and CT material, following guidelines developed by Plante (Plante, op cit.) were made on appropriate slices from each subject's axial-plane library:

1. Full brain volume: Observed asymmetries were expressed with reference to this value, for comparisons across subjects with different brain sizes;
2. LH vs RH hemisphere-volume asymmetry;

3. Peri-Sylvian asymmetry: The width and anterior-posterior length of cortical areas on the upper and lower banks of the Sylvian fissure were measured, using all axial-plane slices where the fissure was visible; the series of two-dimensional measurements was used to calculate a single volume measure for each hemisphere.

Both types of asymmetry volume measures were expressed as difference ratios = [(L-R)/(L+R)]100.

Results. Individual data for whole-hemisphere volumes and periSylvian volumes are presented in Table III. Presentation order is according to periSylvian asymmetry, ranging from the largest Right Hemisphere Advantage (RHA), presented by subject PR (periSylvian 4.9 RHA), to the largest LHA, observed in subject MG (periSylvian 13.0 LHA). Again, the three patients are underlined.

These two measures are combined in a graph of the same results (Fig. M1), arranged in order by: (Panel A) increasing periSylvian LHA (values from Table III are multiplied by 10 for comparison on the same scale as other variables), or (Panel B) sidedness categories. Note that the related literature (cf. Plante, op cit.) focuses on a "typical" pattern of whole-hemisphere RHA vs. periSylvian asymmetry LHA as seen in individuals who are right sided -- however, only one of our pRfR subjects has this pattern (subject AB); the five others with the same sidedness characteristic have a variety of MRI patterns (Fig. M1, Panel B). The data in Panel B indicate that the only sidedness group with a consistent MRI pattern comprises the six individuals who are characterized as personal right, but from left-sided families (middle section on Fig. M1, panel B): all six have periSylvian asymmetries favoring the left hemisphere.

Comparison between MRI and other individual data, such as ear advantages, will be detailed in a later section.

Table III. MRI measures of whole-hemisphere and periSylvian asymmetries.

Initials	Whole-hemisphere	periSylvian
PR	1.3% RHA*	4.9% RHA
JL	0.7% RHA	4.0% RHA
WB	1.0% LHA	4.0% RHA
JLM	0.5% LHA	0.9% RHA
JS	0.6% RHA	0.3% RHA
SHB	0.05% RHA	0.7% LHA
CJS	0.4% LHA	1.0% LHA
AB	5.0% RHA	2.0% LHA
CB	0.4% RHA	3.0% LHA
HR	1.3% RHA	3.1% LHA
MAB	1.6% LHA	6.7% LHA
SJ	0.1% RHA	7.0% LHA
EE	2.0% LHA	7.5% LHA
ES	0.6% LHA	8.0% LHA
MG	0.1% LHA	13.0% LHA

*for purposes of graphing, all values will be multiplied by 10

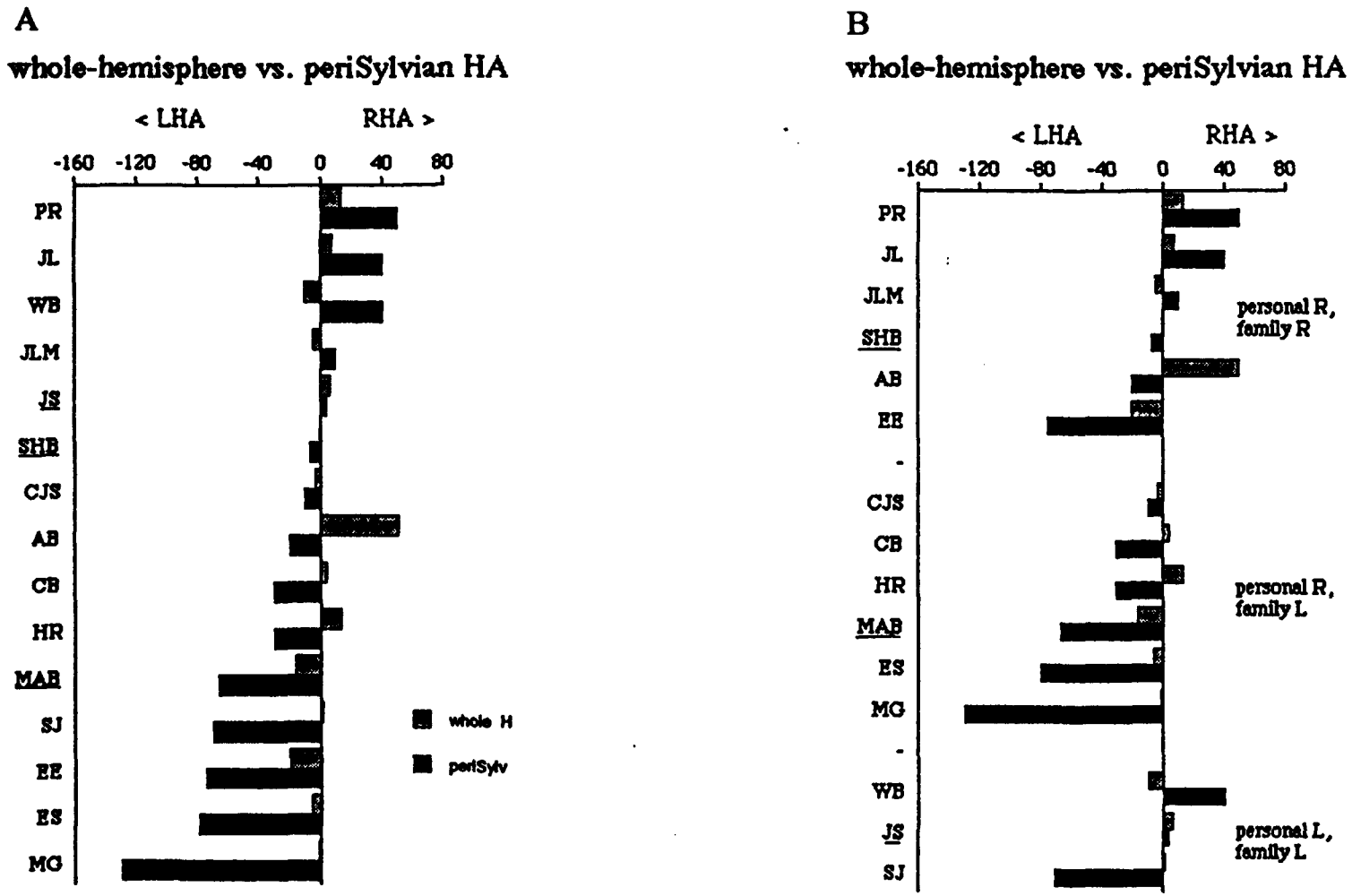


Figure M1. Panel A. Whole-hemisphere and periSylvian hemisphere advantages (HAs) measured in 15 subjects, arranged in order according to periSylvian HA magnitude and direction, from largest right-hemisphere advantage (RHA) at the top, to largest LHA at the bottom. Only one subject (AB) shows the pattern reported in the literature to be "typical" of right-sided individuals, with a whole-hemisphere RHA combined with periSylvian LHA. Panel B. The same data as in Fig. M1, but arranged according to sidedness categories for the 15 subjects. Note that there is no anatomical-asymmetry configuration involving both whole-hemisphere and periSylvian asymmetry, which is typical of any of the sidedness categories, at least as represented by these 15 individuals.

D. Electrophysiology I: Evoked Potentials (EPs)

During the period of AFOSR 88-0352 our work with repeated-measures evoked potentials (REPs) begun previously (Lauter and Loomis 1986, 1988) continued in parallel with the CNS Project, though without specific support from this grant (for example, experiments were conducted via collaborations with other institutions which provided both test equipment and personnel). Appendix D presents a summary of these activities, including reprints, texts of meeting presentations, and two unpublished clinical studies. For the purposes of this report, results of a conventional measure of evoked-potential asymmetry will be described for each of the subjects.

Other authors have described several dependent variables derived from evoked potentials which can serve as measures of sensory-system asymmetries. For example, for brainstem levels of the auditory system, Levine & McGaffigan (1983) and Berlin and colleagues (Berlin et al 1984) have suggested a number of indices of physiological asymmetries, based on standard auditory brainstem response (ABR) protocols. For this report, one of these, the difference in amplitude of ABR peak III comparing left-ear vs. right-ear monaural click series, will serve to characterize subcortical asymmetries in each of the subjects. (A brief discussion of how measures of ABR stability drawn from our separate REPs research [cf. Appendix D] compare with these absolute measures is included in Section III below.)

Methods. Each subject was tested in a single session for auditory-brainstem responses (ABRs) using a Nicolet CA-2000 system. Electrodes were placed at vertex (active), both earlobes (references), and forehead (ground); impedances were checked before, during, and following testing to ensure values were maintained at or below 5 kohms. Condensation clicks were presented at a rate of 11.1 per second, at a level of 80 dB HL. Waveforms representing averages of responses to 2000 sweeps each were collected in the following number and order: four during right-ear, four during left-ear, and eight during binaural clicks (the multiple-waveform protocol was chosen to support a separate repeated-measures analysis). For monaural presentations, vertex activity referenced to both ipsilateral and contralateral earlobes was monitored; only the ipsilateral values will be reported here. For binaural presentation, vertex was referenced to linked earlobes.

For this report, analysis of the resulting data consisted of: 1) identification of peak III on all monaural waveforms, 2) measurement of the mean peak-to-valley amplitude of peak III in response to left-ear clicks, averaged over the four left-ear waveforms collected per subject; 3) measurement of the same value for right-

ear conditions; and 4) calculation of the peak-III absolute-amplitude asymmetry expressed in terms of a percent-difference, i.e., [(L-R)/(L+R)] x 100.

Results. The resulting measures of brainstem asymmetries are presented graphically in Fig. E1, with subjects arranged by sidedness category (no ABR data were available for subject JLM). These asymmetries seem to fall into two magnitude classes across the 14 subjects tested: 1) peak-III amplitude asymmetries that represent less than a 10% difference between responses to the two monaural conditions; and 2) asymmetries that are approximately 18% or greater. While the two classes of asymmetry magnitudes are equally represented numerically in the 14 subjects (7 subjects have smaller than 10% difference, 7 have 18% difference or greater), they do seem to be distributed unevenly by sidedness category: only 1 pRfR subject (AB) has a peak-III asymmetry smaller than 10%, while half of the pRfL and all of the pLfL subjects show similarly small asymmetries. Note also that of the brainstem asymmetries larger than 18%, about half represent left-ear advantages (PR, JL, CJS, and HR), and half favor right-ear input (SHB, EE, CB). Comparison of these results with the other measures in these subjects, including asymmetries based on differences in peak-III amplitude stability, will be presented in Section III.

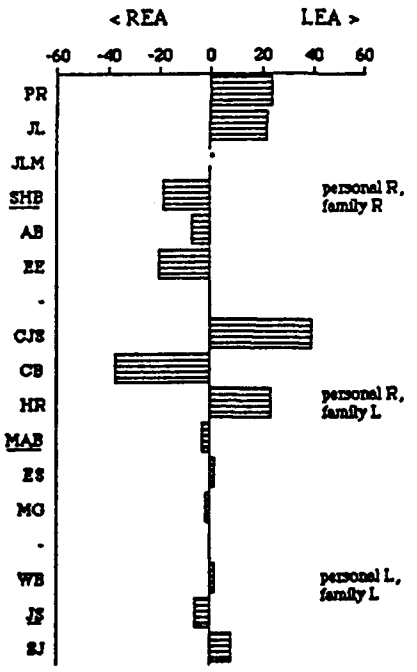


Figure E1. "Brainstem ear differences" expressed in terms of a percent difference comparing ABR peak III amplitude under right-ear vs. left-ear stimulation conditions. Among these subjects, those from left-sided families tend to have smaller brainstem EAs.

E. Electrophysiology II: quantitative Electroencephalography (qEEG).

Methods. The qEEG series of tests were done on a Cadwell Spectrum 32 system at the Brain Mapping Laboratory, a private-practice office located in Tucson. This laboratory provided data collection and access to analysis facilities for the Project on a fee-for-service basis at the rate of $360 per session.

Data collections were scheduled for one half-day session per subject. The subject was fitted with an electrode cap, and electrodes placed at five positions over each hemisphere, including T3/T4. After impedances were checked to ensure low values at all recording locations, the subject relaxed with eyes closed, and ongoing EEG was monitored under a series of conditions (see below). In each auditory-stimulation condition, the subject was asked to mentally label the sounds, as though preparatory to making the keyboard response in the earlier behavioral testing. For monaural conditions, this instruction directed attention to the stimulated ear; for dichotic conditions, attention was directed to different ears on successive blocks. Conditions were tested in the following order:

1) control (no input)
2) right-ear syllables
3) left-ear syllables
4) dichotic syllables [subject will be asked to mentally label the right-ear sounds as in dichotic testing]
5) dichotic syllables [subject will be asked to mentally label the left-ear sounds]
6) control
7) right-ear 200ms-IOI tone patterns
8) left-ear 200ms-IOI tone patterns
9) dichotic 200ms-IOI tone patterns [i.e., tone patterns in the left ear, chords in the right: subject will be asked to mentally label the left-ear sounds as in dichotic testing]
10) dichotic 200ms-IOI tone patterns, with patterns in right ear; subject will be asked to mentally label the right-ear patterns
11) control

Approximately 5 minutes of EEG was collected under each condition, for a total of 11 x 5 min., or approximately 1 hour actual stimulation time.

For data analysis, the Cadwell Spectrum 32's editing software was used to select by eye 48 artifact-free 2.5-second epochs of EEG for each condition for further analysis; these epochs for each condition were then subjected to spectral

analysis re four bandwidths (delta 1.5-3.5 Hz; theta 3.5-7.5 Hz; alpha 7.5-12.5 Hz; beta 12.5-20 Hz); and the results tabulated in terms of: absolute power, relative power, power asymmetry, and power coherence (sample print-out in Fig. E2).

Name: Lauter, Judith Date: 06/07/88
Age: 44.0 yrs # Epochs: 48 Time: 10:54:42

Monopolar Raw Measures

		Fp1	Fp2	F7	F8	F3	F4	C3	C4	Fpz	Fz	Cz
Absolute Power (uV²)	Δ	6.2	5.8	4.4	3.9	7.0	6.5	6.1	5.8	6.1	7.6	7.6
	θ	6.9	6.6	4.3	3.5	7.7	7.1	7.5	6.8	6.9	8.4	8.2
	α	8.6	8.2	6.6	5.3	10.3	10.1	15.2	12.0	8.6	11.5	11.4
	β	8.6	8.0	6.2	4.6	11.6	10.2	9.2	8.7	8.4	11.7	9.4
	T	29.4	27.7	21.6	17.5	36.7	34.0	38.1	33.6	29.1	39.4	36.8
Relative Power (%)	Δ	21.1	21.0	20.3	22.6	19.2	19.2	16.0	17.5	21.1	19.4	20.6
	θ	20.3	20.4	20.1	20.2	20.9	20.8	19.7	20.4	20.3	21.3	22.3
	α	29.2	29.7	30.7	30.6	28.1	29.6	39.9	36.9	29.5	29.3	31.2
	β	29.2	28.8	28.8	26.3	31.6	30.2	24.3	26.1	28.9	29.8	25.5
Power Asymmetry (%) [L-R]	Δ	3.1		4.9		3.5		1.8				
	θ	2.5		10.1		4.0		4.4				
	α	2.0		10.5		1.1		11.4				
	β	3.6		14.0		6.0		2.6				
Coherence (%)	Δ	95.1		48.1		93.0		88.3				
	θ	92.0		37.3		89.0		77.3				
	α	95.0		42.2		86.5		42.6				
	β	91.5		48.4		79.5		32.7				

		T3	T4	T5	T6	P3	P4	O1	O2	Pz	Oz
Absolute Power (uV²)	Δ	2.3	2.8	3.1	2.6	5.2	4.9	3.8	2.7	6.1	2.7
	θ	3.5	3.8	3.8	2.7	6.0	5.6	3.2	2.8	6.6	2.9
	α	8.4	7.0	10.0	5.9	13.3	10.6	6.5	6.5	11.0	5.0
	β	4.7	9.7	7.4	4.6	8.4	7.1	7.4	6.1	8.2	5.0
	T	19.6	22.7	24.4	15.0	33.0	28.2	21.1	18.3	32.0	17.3
Relative Power (%)	Δ	14.0	12.3	12.7	16.4	15.0	17.5	18.3	14.0	18.7	15.6
	θ	18.1	13.4	15.6	17.3	18.1	19.0	15.3	15.7	20.1	16.7
	α	42.9	31.0	41.0	37.1	40.4	37.5	31.0	35.9	35.9	33.6
	β	24.1	42.0	30.5	28.9	25.5	25.0	35.1	33.4	25.0	34.0
Power Asymmetry (%) [L-R]	Δ	0.4		0.0		2.7		17.7			
	θ	7.5		16.1		3.3		5.0			
	α	0.9		25.9		11.3		-0.1			
	β	-34.4		23.6		0.5		9.6			
Coherence (%)	Δ	35.3		63.3		90.5		83.3			
	θ	12.9		44.9		83.4		87.6			
	α	16.4		15.3		66.3		76.6			
	β	12.2		6.9		60.4		67.3			

Δ = 1.5 - 3.5 Hz
θ = 3.5 - 7.5 Hz
α = 7.5 - 12.5 Hz
β = 12.5 - 20 Hz

Figure E2. Sample print-out of qEEG data based on monopolar-referenced electrode arrays (each indicated location referenced to linked earlobes) provided by the Cadwell Spectrum 32 "brain mapper." The table summarizes the array of values representing EEG patterns observed during a single test condition (e.g., resting), by averaging 36 2.5-sec artifact-free epochs selected by eye. Values are cited by electrode location, and include absolute power, relative power, power asymmetry, and coherence. The latter two measures are calculated for the indicated pairs of electrodes.

Results. Examination of early findings (Lauter, In Press) indicated that during auditory-stimulation testing, the one of these variables which showed the most systematic change was power asymmetry in the beta bandwidth as recorded over auditory-cortex electrode locations (T3 and T4). Thus T3/4 beta-power asymmetry was chosen as the dependent variable for these tests.

Sample results for all 11 conditions for subject JL are presented in Fig. E3 using a "hemisphere advantage" display similar to the format developed for examining relative ear advantages (Lauter, op cit.). For the qEEG data, the graph is based on a continuous dimension of "hemisphere advantage," in this case, plotting the interhemispheric asymmetry in beta-bandwidth power comparing electrode locations T3 and T4, as a function of test condition. As with the behavioral asymmetries (Fig. B1), the qEEG asymmetry is calculated as percent difference = [(beta absolute power in uV over T3 minus the same value over T4) divided by (the sum of the two values)] x 100. Values of T3/T4 beta power asymmetry observed during the three spaced control conditions are plotted on the top line, monaural conditions next, and dichotic conditions on the line below this. On the lowest line are plotted JL's behavioral results in terms of ear advantages taken from Fig. B1, but graphed here as though reflecting predominant activation in the opposite hemisphere--14% REA for the syllables (plotted at 14 on the LHA side of the scale) and 14% LEA for the tones (plotted at 14 on the RHA side of the scale).

Note first that for this subject, none of the test conditions evoked a T3/T4 beta power asymmetry favoring the left hemisphere: under all conditions tested on this individual, the index of asymmetry favored the right hemisphere. However, within each set of stimulation conditions, the patterns of "relative hemisphere advantages" are consistent with principles of asymmetry based on side of space and on sound characteristics.

1) During the control conditions, note that the values of T3/T4 beta power resting asymmetry do not stay the same throughout the session: for this subject, the resting asymmetry begins at 34% RHA, shifts leftward to 24% RHA following the four blocks of syllables, then shifts rightward to 41% RHA following the four blocks of tone patterns. We will return to the significance of these changes in resting asymmetry in a moment.

2) With monaural listening, T3/T4 beta power asymmetry consistently favors the right hemisphere. However, the relative values of the asymmetry, considered from condition to condition, seem to be affected by both of the principles of asymmetry discussed above. First, side of space: when sound is held constant, the right-ear conditions evoke asymmetries to-the-left of those evoked in the left-ear conditions. Second, sound characteristics: when ear is held constant, the

conditions involving listening to syllables evoke asymmetries to the left of those involving listening to the tone patterns. The effect of sound characteristic is less apparent for the right-ear conditions than for the left (beta-power asymmetry values for "SR" and "TR" conditions are virtually identical), although this cannot be tested statistically since there is only one asymmetry value representing each condition.

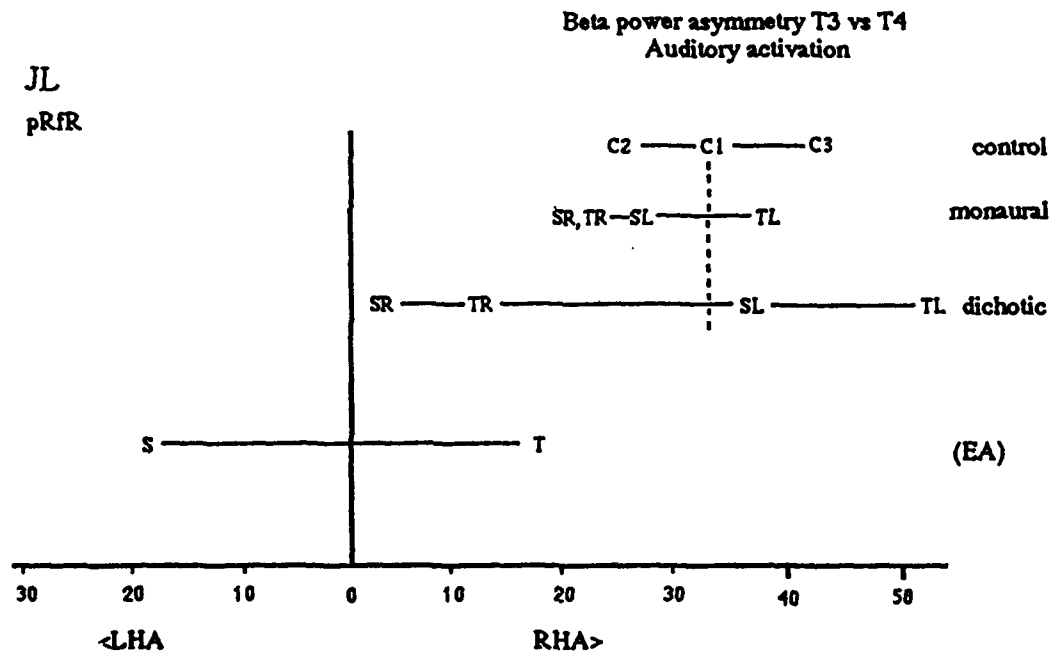


Figure E3. "Hemisphere advantages" observed in subject JL during 11 test conditions tested with qEEG. Values are in terms of percent-difference power-asymmetries in the beta band comparing electrode locations T3 vs. T4, recorded during spaced resting (top row), monaural (middle) and dichotic conditions (lower qEEG row). The bottom pair of values represent the ear advantages measured behaviorally, plotted as though they reflect specialized processing in contralateral cortex.

3) During dichotic listening, the two types of asymmetry are even more dramatically distinguished than in monaural, and the hypothesized additive combinations of ear and sound clearly evoke the extremes of hemisphere advantages: dichotic tone patterns attended in the left ear yield the most extreme right-hemisphere advantage of any condition tested, and dichotic syllables attended in the right ear evoke the most extreme leftward hemisphere advantage of any condition, though, as noted, even this condition does not evoke an actual LHA for this subject.

4) There is a good match between the relative asymmetries for the two sounds observed behaviorally (the "EA" scores, lowest line on the graph) and those observed with qEEG (e.g., the dichotic "SR" and "TL" values): in both cases, the tones evoked an asymmetry that was "toward-the-right-hemisphere-of" the asymmetry for the syllables--in spite of the fact that the actual asymmetries do not match: split EAs behaviorally, both RHAs under qEEG.

Before proceeding to consider the results for the other subjects, two details of JL's data need to be discussed. The first is the shift in the resting asymmetries, from control scan #1 (C1) to C2 to C3. At first glance, the degree of inconsistency here is disturbing; however, consideration of the chronological sequencing of the control scans suggests that the resting asymmetries in fact reflect the effects of preceding stimulation: C2 shifts away from C1 in the same direction as the extreme asymmetry evoked by the syllables (i.e., diminished RHA), and C3 shifts away from C2 in the same direction as the extreme asymmetry evoked by the tone patterns (i.e., enhanced RHA). Aside from consideration of what this may indicate regarding underlying brain mechanisms, the change in resting asymmetry over the course of the test session emphasizes that one must be very careful in defining "control condition."

The second detail is the observation that while there is a good behavioral/qEEG match in relative asymmetries for the two sounds, the absolute asymmetries (split EAs vs. two RHAs) do not match. This observation combined with the preceding one regarding resting asymmetries suggests that a more accurate picture of asymmetries evoked during task performance might be obtained if the stimulation asymmetries were normalized with regard to the underlying "bias" of the system as expressed by the initial resting asymmetry.

In order to do this, we borrowed a strategy from PET data analysis, in which it has been found (cf. demonstrations in Lauter et al 1985, 1988) that by analyzing changes in the level of activity in regions of interest, comparing resting control vs. activation conditions, one can obtain a measure of brain response that is more sensitive to stimulus and task manipulations than are "snapshot" values representing brain activation in a temporally local way. For

the qEEG data, the calculation amounts to considering the initial resting asymmetry value shown in Fig. E3 as something like a "DC offset," and "sliding" the zero line along the horizontal until it coincides with this value, at 34.4 on the RHA side of the dimension. With this adjustment, and considering only the extreme qEEG scores (dichotic "SR" and "TL"), it can be seen that these two scores are now distributed as "split" hemisphere advantages, much more like JL's behavioral pattern, with the qEEG asymmetry for the "SR" condition now at 31.9 LHA (cf. behavioral 14 REA), and for the "TL" dichotic condition at 18.3 RHA (cf. behavioral 14 LEA).

Similar effects were observed for the other 14 subjects. Data for resting asymmetries are presented in Fig. E4, arranged according to sidedness characteristics. Note that on this measure, as in the MRI periSylvian data, the group identified as pRfL (middle set of subjects) shows the most consistency, with a resting qEEG asymmetry favoring the left hemisphere in all but one of these individuals; more complete comparisons of the MRI and qEEG resting data will be presented in a later section.

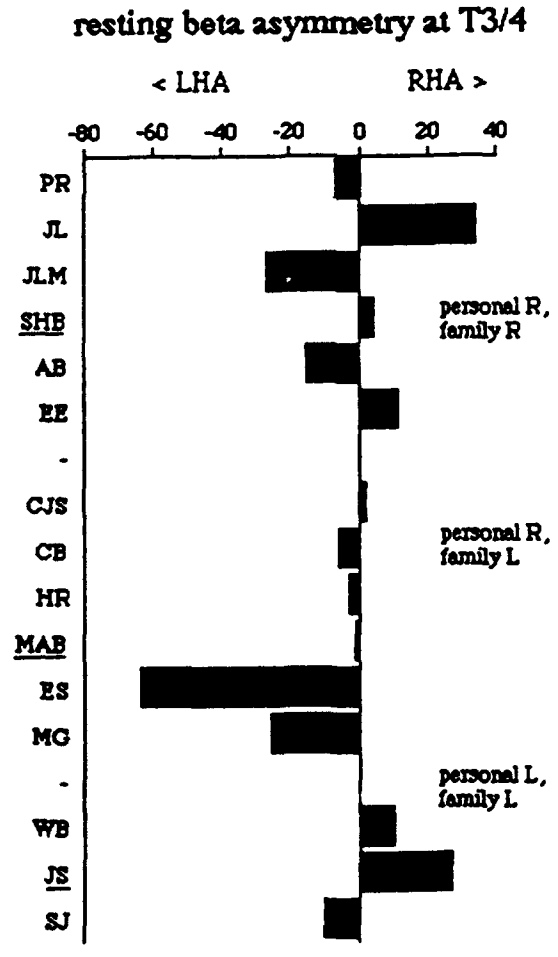


Figure E4. Resting qEEG hemisphere asymmetries (HAs) for 15 subjects, representing data collected during the initial rest condition in each individual's qEEG session.

qEEG symmetries for the right-ear/dichotic syllable condition and the left-ear/dichotic tones are plotted in Fig. E5, using values "normalized" re each subject's resting asymmetry according to the method described above for JL's data. Note that although none of the sidedness groups seems to show any consensus with regard to HA for the syllables, the HA pattern for the tone patterns is much more consistent in all three subject classes: tone patterns evoke a RHA in 4/6 of the pRfR and all of the pRfL individuals, for a total of 10 tone-pattern RHAs of the 12 personal-right subjects); and tone patterns evoke a LHA in all three personal-left subjects.

Finally, there is a striking degree of agreement in patterns of qEEG asymmetries across these subjects in terms of relative HAs: for most, the HA for the syllables is to-the-left-of the HA for the tones. This is true even in cases where both sounds evoked a LHA (e.g., subject WB) or both evoked RHA (e.g., EE). Only four of the 15 have a "reversed" pattern: PR and JLM (both reportedly pRfR), and MG and SJ (both from left-sided families). In a later section we will compare the behavioral and qEEG asymmetries observed for the two sound sets in each subject.

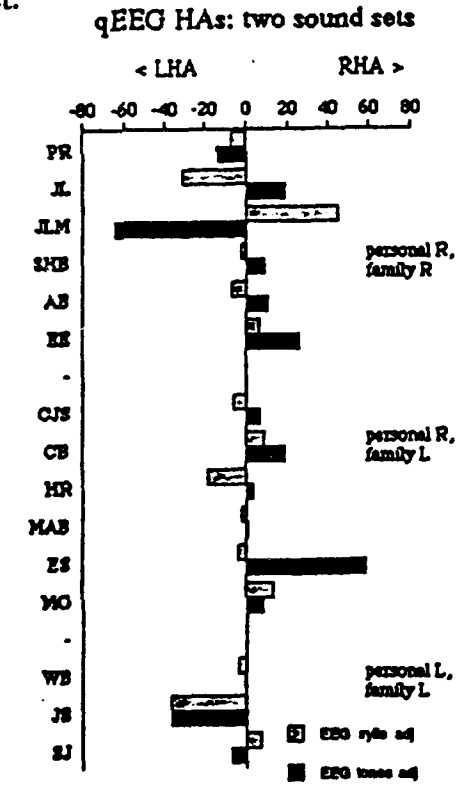


Figure E5. qEEG HAs for two conditions: right-ear attention to dichotic syllables, and left-ear attention to dichotic tone patterns. Note the lack of a consistent pattern in any of the sidedness groups, combined with a general consensus in terms of "relative HAs" in all but four cases: the syllables evoke a HA that is to-the-left of the HA for tones. (Values are normalized for each subject with reference to the "sidedness bias" taken from the initial resting condition: see text for details.)

F. Magnetoencephalography (MEG) and Positron Emission Tomography (PET)

Due to truncation of the projected third year of funding, no support was available from AFOSR 88-0352 to provide travel expenses to Los Alamos for MEG testing or to Knoxville for PET, nor were there funds with which to pay the fee-for-service required for PET. However, some progress was made with regard to both types of testing, which together ensure a basis for related future activities in the CNS Project.

MEG. The PI retained Collaborator Status with LANL throughout the period of AFOSR 88-0352. Concurrent with the first year of the grant, there was a change in CNS Project contact personnel at Los Alamos. Dr. Don Sinex, who had served as our liaison there during previous years, left to take a position at Boys Town Institute, and the division at LANL which he had directed was completely reorganized. However, at the same time, an expert in electrophysiological measures of brain asymmetries, Dr. Chris Wood, joined the LANL division which had direct oversight of the MEG facility.

Correspondence and conversations with Dr. Wood, including a talk during the Neuroscience meeting at Phoenix in 1988, revealed that he and the PI share many interests and philosophies about human brain organization related to asymmetries. Dr. Wood has expressed his enthusiasm about collaborative MEG work with the PI, including experimental designs such as those represented by the MEG component of the CNS Project. He has also provided documentation that these designs fall within the protocols already authorized for use with normal adult subjects by the LANL IRB. Complicated work schedules for the PI and Dr. Wood, together with a lack of travel funds, have precluded initiation of pilot experiments, but as soon as funds become again available, it is expected that all factors necessary for enabling the start of these experiments will be in place.

PET Introduction. Over the period of AFOSR 88-0352, the PI has pursued a number of activities related to research with PET. These include: 1) continuing analysis of PET data previously collected by the PI during 1981-1985 at the Mallinckrodt Institute of Radiology PET center in St. Louis, using a data-analysis station funded by AFOSR 87-0003 (see c.v. for reports of these data); 2) a number of local, national, and international presentations describing experimental results and the research potential of PET applications to studying physiological correlates of human behavior (see c.v.); 3) establishing working relationships with personnel at a number of PET facilities around the country (University of Wisconsin at Madison WI, Good Samaritan Hospital in Tempe AZ, and the University of Tennessee Medical Center in Knoxville TN); and 4) collecting new

data, primarily at the UTMCK center.

Due to the state of site development at the Wisconsin and Arizona facilities, recent efforts have been focused on pursuing a collaborative interaction with personnel of the PET facility at the University of Tennessee Medical Center at Knoxville. Relevant activities included:

1) an invited lecture by the PI on "Positron emission tomography as a tool for studying normal human brain function," presented to a UT campus-wide audience including members of the UTMKC PET center in 1988;

2) an address on "Relevance of studies in normal subjects to clinical applications of PET," given to a UTMCK-sponsored nationally-advertised conference on "Clinical PET: When? How? Where?," in 1989;

3) completion of a proposal to the UTMCK IRB covering PET studies with CNS-Project-like designs, which eventually served as the basis for the UTMCK PET Center's IRB approval for all normal adults (1989-90);

4) work with a doctoral student at the University of Tennessee's Department of Audiology and Speech Pathology on a dissertation using PET to study brain responses to speech stimuli (data collection for those experiments is completed as of 12/91, and analysis is underway); and

5) two pilot test sessions designed to prove the UTMCK's PET center's capability to conduct multi-scan series such as those required by the CNS Project (i.e., eight intravenous injections of oxygen-15-labelled water of 55-80 mCi per injection at approximately 15-minute intervals).

PET Methods. The first of the two pilot sessions was devoted to quantification of responses to controlled hand movements; this type of activation was chosen based on previous work by the PI on PET responses to hand flexion, which had indicated that this type of movement results in clear, highly localized, asymmetrical responses. For this pilot session, bimanual as well as unimanual conditions were tested to mimic the side-of-space and hierarchical conditions which would be included in later auditory experiments, and spaced resting conditions were also scheduled, to allow for observations of the intermediate-term "perseveration" effects we have noted previously in both PET and qEEG data. A complete report of the methods and results of this experiment are included in Appendix C (Lauter et al 1990).

The second PET pilot session conducted at UTMCK made use of the experimental design from the original CNS Project proposal; the PI served as the subject. Preparation for testing was based on procedures developed in the PETT-VI laboratory at the Mallinckrodt Institute of Radiology in St. Louis during the PI's tenure there, including: 1) placement of insert-receiver earphones for sound delivery (Heidbreder & Lauter 1983), 2) fitting of a face mask to hold the head in

place during testing, and 3) insertion of an intravenous cathether for isotope administration (oxygen-15-labelled water).

During each scan, visual input was limited by having the subject lie quietly with eyes closed, with gauze pads taped over the eye holes of the face mask, and the room darkened. Ambient noise was limited to computer noise and the sounds from the air-conditioning equipment.

Data collection was accomplished on a CTI-Siemens 15-slice tomograph, in a two-hour session characterized as an eight-water, 15-slice study. Conditions were tested in the following order: 1) control scan (no input), 2) stimulation scan with syllables presented monaurally to the right ear; 3) stimulation scan with dichotic syllables and attention to the right ear, 4) stimulation with dichotic syllables and attention to the left ear 5) control scan, 6) dichotic tone patterns with left-ear attention, 7) dichotic tone patterns with right-ear attention, 8) control scan. All sounds were presented at a comfortable listening level, i.e., similar to the setting used in prior behavioral testing. On stimulation runs, sound presentation was begun approximately 1 minute prior to isotope injection, and continued throughout the 40-sec scan.

The PET data files were analyzed on a SUN graphics workstation at the UTMCK image-analysis facility, using software developed by CTI. Quantitative analysis of responses at several levels of the auditory system (cf. Lauter et al 1985) were made, including observations of response asymmetries, expressed as "relative hemisphere advantages" for the different test conditions (control, and two sound sets).

Selection of regions of interest (ROIs) representing three posited levels of the central auditory system was made by visual examination of the resulting slice series, according to guidelines developed in earlier research (Lauter et al 1988) for estimating auditory levels based on appearance of quasi-anatomical landmarks: shape and extent of the cerebral ventricles, and "edge artifacts" associated with medial temporal/lateral frontal lobe abutment, cingulate gyrus, and calcarine fissure.

The three levels estimated were: thalamus (presumably reflecting responses in a combination of medial-geniculate nucleus plus pulvinar: Lauter et al 1988), primary-auditory cortex, and "language-cortex level." A schematic representation of the ROIs selected for analysis in each of the conditions is provided in Fig. P1; the selection of each ROI to be analyzed under each condition was made by eye, thus the slight degree of variability in exact locations of each ROI from condition to condition. The software provided number of counts within the selected left- and right-hemisphere ROIs at each level, and hemisphere asymmetry was calculated for each level based on a percent difference comparison of counts in the LH vs. RH ROIs.

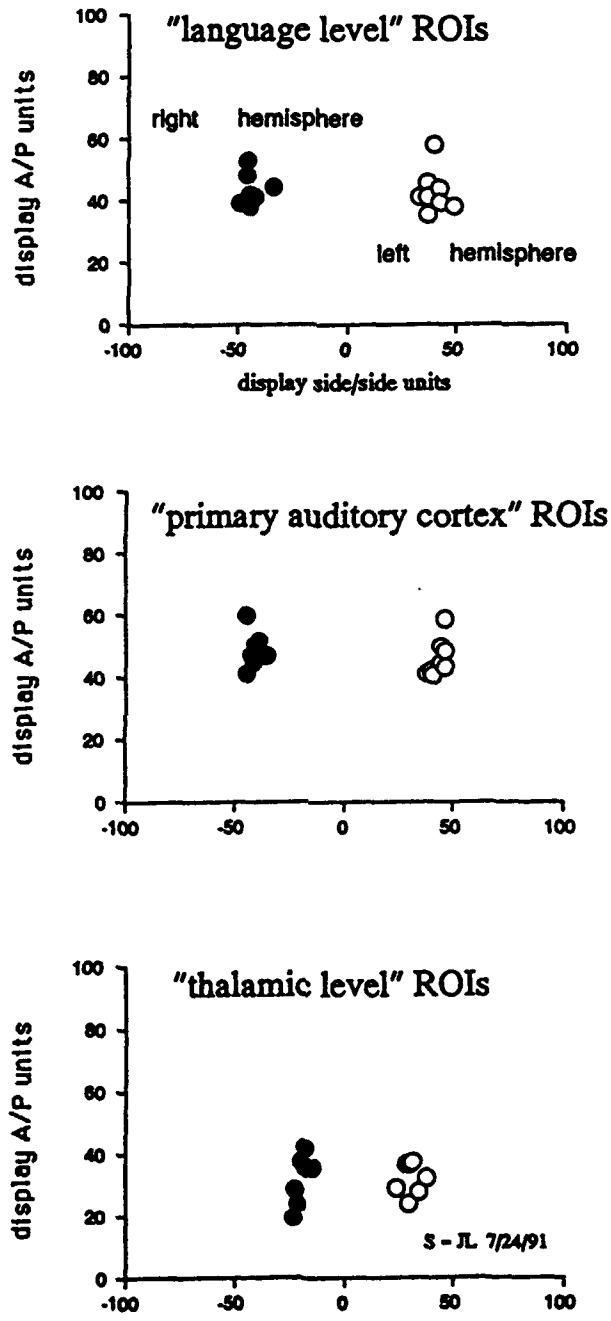


Figure P1. Schematic representation of the location of regions of interest (ROIs) selected to represent responses at three levels of the auditory CNS during a series of resting and auditory-test conditions.

PET Results. Results are presented in Fig. P2, with changes in hemisphere asymmetry as a function of test condition shown separately for each of the three levels.

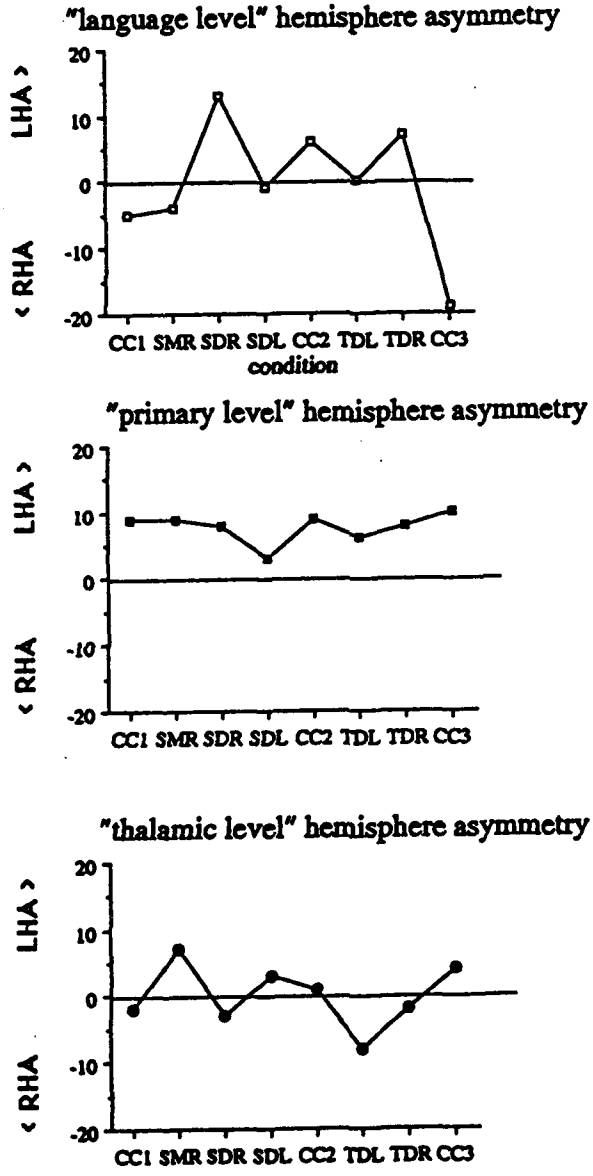


Figure P2. PET hemisphere asymmetries calculated as percent-differences comparing the right- and left-hemisphere ROIs represented in Fig. P1, for each of eight test conditions, observed at each of three levels ("language cortex," "primary auditory cortex," and "thalamic"). Data are for a single subject (JL).

At the "language level" (Fig. P2, top panel), the resting asymmetry was approximately 5% favoring the right hemisphere (5% RHA). The resting asymmetry was maintained during the first Syllables Monaural Right (SMR) test condition, but changed dramatically in response to the Syllables Dichotic Right (-ear attention) condition, to become a 13% LHA, which is appropriate given the assumed effects of: 1) side-of-space (right-ear attention should generate a contralateral LHA), combined with 2) stimulus-based specialization (the synthetic stop CVs with their cluster of "LH dimensions" (Lauter 1983) should generate a LHA in this pRfR subject). Although in the two subsequent dichotic conditions involving attention to the left ear (SDL and TDL), there is no RHA invoked, the direction of change is certainly toward-the-right-hemisphere-of the extreme score for the SDR condition (a pattern reminiscent of the qEEG scores for this subject -- cf. Fig. E-2; this comparison will be further examined below).

There are also instances of "residual effects" and in one case, "overshoot" to be seen in these data which were seen in both the qEEG results (see that section), as well as the findings on the PET hand-movement study (Appendix C). Specifically, the initial resting asymmetry of 5% RHA is shifted following stimulation with the syllables to 6% LHA (condition CC2), and in the opposite direction, to 19% RHA, following stimulation with tone patterns (condition CC2). A graphic representation of asymmetries observed at the "language level" under all eight conditions is provided in Fig. P3, using a format similar to that employed for the qEEG results (Fig. E3).

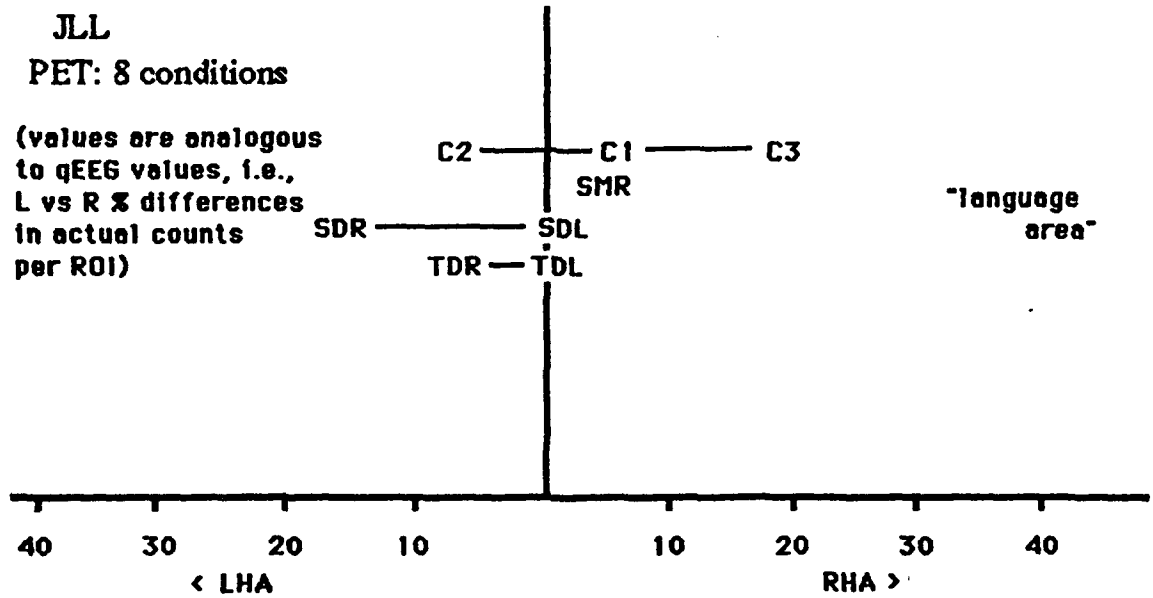


Figure P3. Changes in "language-cortex level" PET response as a function of change in test condition, using a format similar to that of Fig. E3.

At the other two levels studied, somewhat different patterns of response are seen, presumably reflecting the influence of variables other than hemisphere specialization (cf. Lauter et al 1988). For example, at the "primary level," (Fig. P2, middle panel) a small initial resting 9% LHA is maintained throughout all conditions (8-10%), and is little affected by any of the stimulation conditions. The small changes which do occur (down to a 3% LHA and a 6% LHA) are seen during the two left-ear conditions (SDL and TDL, respectively), and represent shifts in the appropriate direction., i.e., diminished LHA. This combination of an insensitivity to stimulus type (related to hemisphere specialization) plus a clear effect of side-of-space is similar to previous observations made with PET at this level of the auditory system (Lauter et al 1985, 1988).

At the "thalamic level" (Fig. P2, lower panel), an initial resting asymmetry of 2% RHA varies somewhat around 0HA (from 3% RHA to 4% LHA) throughout the session. The extreme changes occur only when stimulation follows a resting condition: for the first syllable block (SMR), in which the thalamic asymmetry shifts appropriately from a 2% RHA to a 7% LHA, and for the first tone-pattern block (TDL), with an appropriately opposite shift in asymmetry to favor the RHA (8% RHA). This observation of a "novelty-effect" response in the thalamus extends our previous observations (Lauter et al 1988) which were limited to recognition of distinctions at this level based only on monaural vs. binaural input.

Comparison of PET with qEEG results in the same subject. One of the original goals of the CNS Project was not only to exploit the complementarity of the different test methods, but also to make direct comparisons between the versions of brain activation provided by two or more techniques, when comparable testing conditions were available. The most obvious comparison was between two methods which provide somewhat localized physiological data, qEEG (2-3 cm) and PET (5-15 mm). Due to funding limitations, only one subject (JLL) was tested under identical conditions with qEEG (Fig. E3) and PET (Fig. P3).

The data shown in Figs. P3 ("language level" only, as the most direct comparison with the qEEG T3/4 electrode locations) and E3, are re-plotted in a combined format in Fig. P4. The top panel graphs the two sets of values on two scales, one for qEEG (filled symbols) and one for PET (open symbols). Note the striking similarity in the shapes of the two functions -- even though the PET values flux back and forth between actual LHAs and actual RHAs, while the qEEG values (not adjusted to the original resting asymmetry) are all fluctuations in the size of a consistent RHA. Clearly the underlying responses are very similar, even though tested almost three years apart, and are reflected similarly under both test methods.

In the lower panel of Fig. P4, the two sets of values are presented on the same scale. This representation points up a basic difference between the two measures, namely, that the qEEG dependent variable (voltage) seems to have a wider dynamic range than does the PET measure (isotope counts), a distinction which results in more dramatic shifts in the qEEG values as a function of changes in test condition.

If the initial resting "bias asymmetry" is taken into account for both measures, agreement between the qEEG and PET data is even better (Fig. P5). Here, the initial resting (CC1) values from Fig. P4 were set at zero for both methods, and the other scores shifted with relation to this resting bias. As seen in both the top and lower panels of Fig. P5, the fit between the two functions given this adjustment to an initial resting bias is better than without it (cf. two panels of Fig. P4).

A number of observations may be made of these data (concentrating on the lower panel of Fig. P5). First, for the syllable conditions, 1) While both PET and qEEG show an appropriate leftward shift away from resting during the first monaural condition (SMR), the response is much larger in qEEG; 2) both measures show an increased LHA during the SDR condition, and a smaller LHA during the subsequent SDL condition; 3) the distinction between SDR vs. SDL revealed by both methods suggests an additive effect of two principles of asymmetric organization: a larger LHA when both stimulus characteristics and side-of-space (ear attention) favor the left hemisphere, and a smaller one when stimulus is held constant but ear attention is shifted to the left ear.

For the second resting condition (CC2), note that the lower panel of Fig. P5 indicates that the percent-difference HA value is identical for the two tests. Perhaps most of all the values shown, this second resting condition thus provides a cross-test within-subject reliability check: i.e., over three years' time, the zero-adjusted hemisphere advantage during a resting condition following syllable testing in this subject is virtually the same, although it was first quantified using qEEG and three years later using PET.

As indicated in the lower panel of Fig. P5, the two functions continue parallel throughout the rest of the session, for the two tone-pattern conditions and the final resting block. Note the continuing high degree of similarity in the values comparing the two techniques.

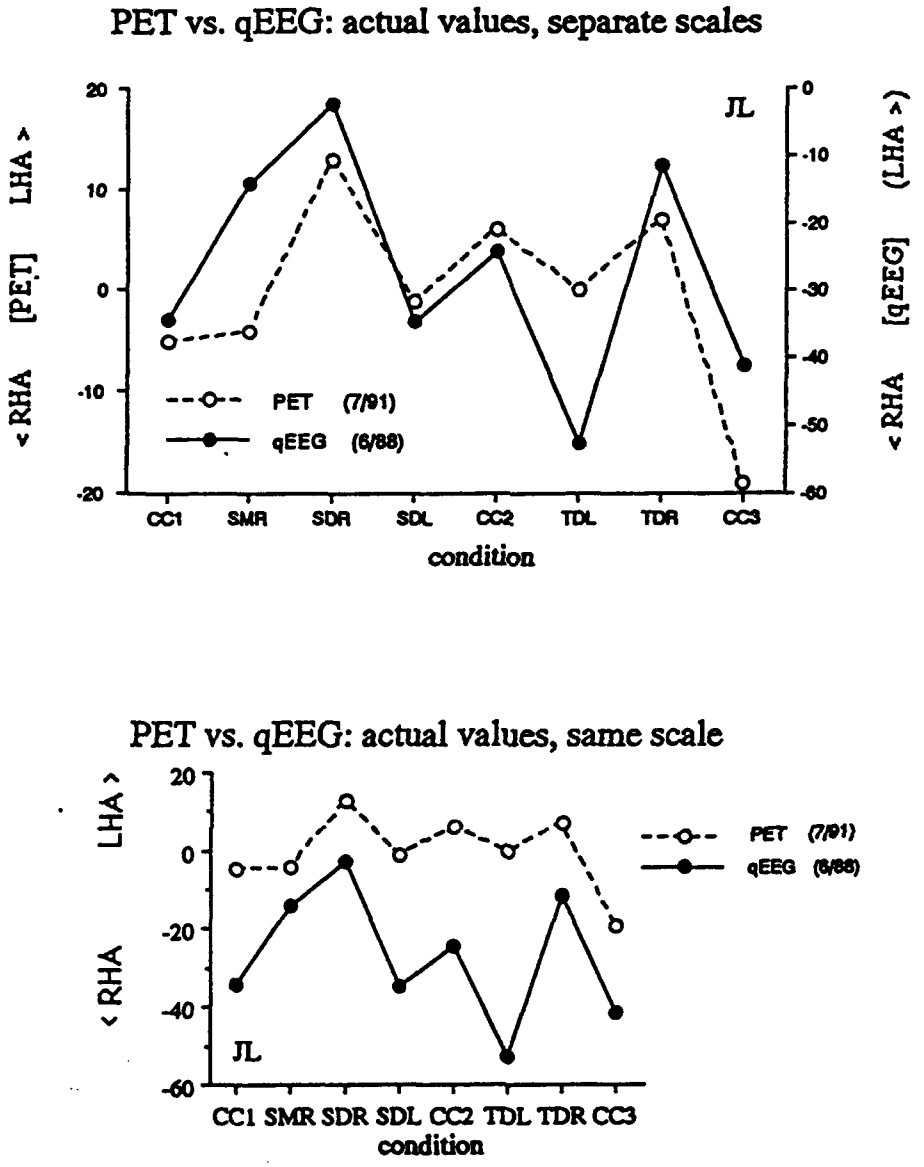


Figure P4. Comparison of hemisphere asymmetries measured with qEEG vs. PET for the same conditions tested in the same subject, approximately three years apart. Values represent hemisphere asymmetries calculated for left- vs. right-hemisphere "language-cortex level" PET ROIs compared with "auditory-cortex" electrode locations (T3/4). Top panel plots the values on separate scales; lower panel plots them on the same scale.

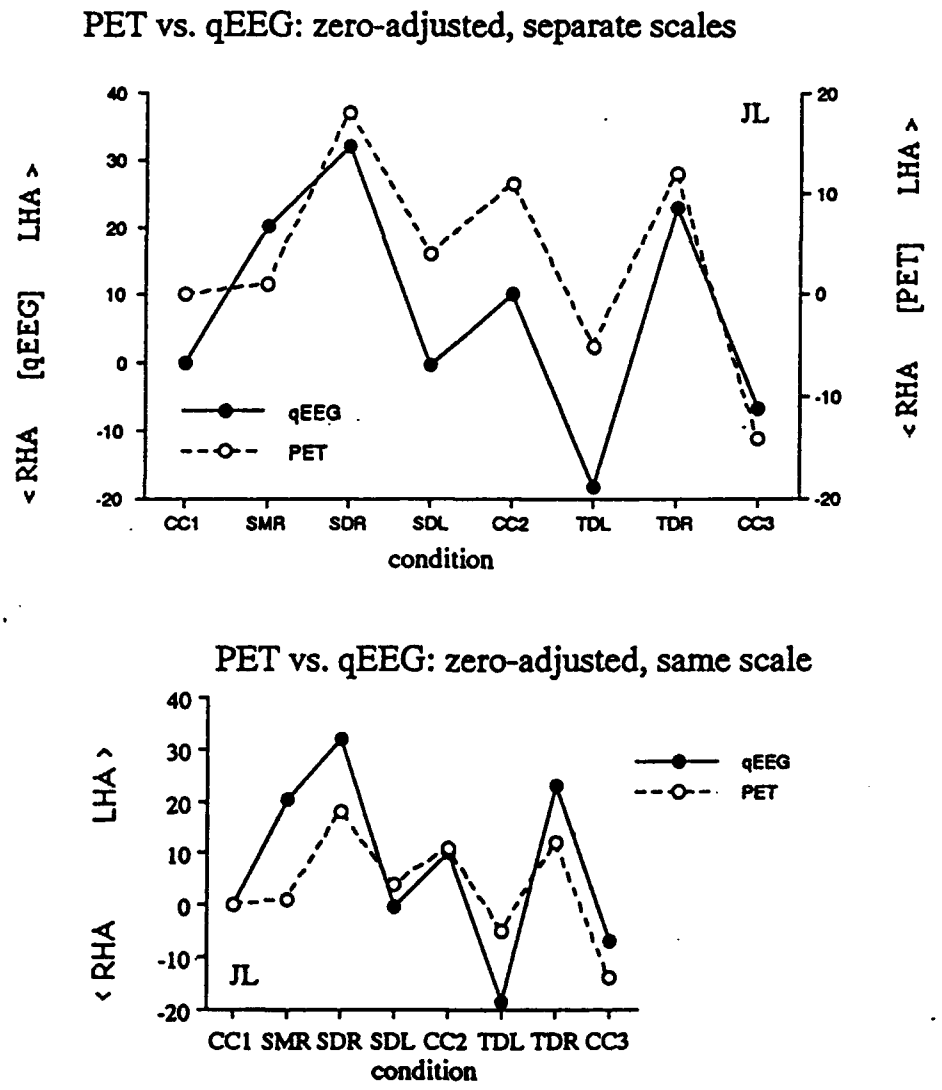


Figure P5. Hemisphere asymmetries measured during a series of conditions with qEEG vs. PET. Same original data as in Fig. P4, but here all conditions after the original resting condition CC1 are "zero-adjusted" with regard to the CC1 asymmetry. Top panel plots the values on separate scales; lower panel plots them on the same scale.

There are several conclusions to be drawn from this comparison. First, the patterns of changes in asymmetries as a function of test condition are comparable in PET and qEEG examined in the same subject. Second, the fact that these patterns show such remarkably good similarity in spite of the fact that the original dependent variables (number of counts generated by a cerebrovascular-borne isotope for PET, power in microvolts-squared of electrophysiological activity for qEEG) are very different validates the use of relative measures in the CNS Project design.

Third, the striking similarity in the PET vs. qEEG patterns, in spite of the fact that the two sets of data were collected three years apart, testifies to the reality of patterns of asymmetries as replicable characteristics of an individual brain. Fourth, the fact that the qEEG measure appears to have a larger dynamic range than is true for PET suggests that qEEG may provide not only a wider space over which responses may vary, but also as a corollary, may make it possible to identify finer distinctions in changes in asymmetries within that space.

In summary, these results comparing PET with qEEG suggest that for some human-neuroscience applications, qEEG may in fact provide a "substitute" for the much more expensive and invasive procedures involved with PET, providing the following advantages: 1) clear effects of experimental manipulations such as side-of-space, stimulus type, and task; 2) clear individual characteristics, associated with other features of each subject (see Section III below); 3) good replication of effects within individuals; 4) comparable if not better sensitivity than PET to stimulus and task manipulations; 5) a wider dynamic range of response than is available with PET; 6) finer distinctions than PET in the step-wise effects of manipulations; 7) freedom from constraints on subject selection (e.g., children) imposed by the radioactivity involved with PET; and 8) allowing of many more within-subject manipulations than is possible with PET given its associated constraints on subject exposure.

Of course the advantages offered by PET of three-dimensionality of response localization, finer spatial resolution in both the horizontal and vertical dimensions, and the access it provides to brain chemistry, render it unique as a tool for human neurophysiology. However, for those experimental questions which can be addressed with both techniques, additional research is required to articulate completely the points of comparison, to identify the circumstances and experimental questions for which each is best suited, and to establish not only the degree of match between results collected with the two techniques, but also clarify the sources of difference, and their significance.

One practical application of these findings in cases where both test results are valuable, may be to generate guidelines for pre-testing with qEEG which could

render subsequent testing with PET more efficient and thus more cost-effective. It is to be expected that further comparisons of qEEG and PET versions of responses in the same brain to the same test conditions, will lead to a more sophisticated understanding of the ways in which these two tests provide unique as well as complementary insights into brain mechanisms underlying behavior.

III. Cross-modality comparions

In the preceding section, we examined individual results on each of the four tests completed on the majority of the subjects: behavoral dichotic listening, MRI, ABRs, and qEEG. However, the premier goal of the CNS Project was to compare test results across modalities, not only to establish the extent to which different measures during the same test conditions resulted in similar patterns (such as the qEEG vs. PET comparison made above), but more importantly, to discover new and perhaps unsuspected relations among the measures. There are clearly a multitude of combinations of two or more of the methods which could be examined. In this section, we will present a selection of those many possibilities, focusing on comparisons which not only reveal the "internal consistency" of results within subjects, but which also provide a basis for subject-grouping derived from patterns of behavioral/anatomical/physiological characteristics.

One comparison has already been treated, as data for each of the test methods have been presented according to subject sidedness characteristics. More insight into sidedness classifications is provided by the combinations of measures examined below.

In order to provide guidelines for these comparisons, values for all measures were subjected to a discriminant analysis, pooled over all subjects as well as considered group by group. Results for three subjects (PR, JLM, and HR) were omitted due to incomplete data. Table IV presents a list of the three pairwise variable combinations which the test indicated had within-class correlation coefficients which were significant for the pooled data at the .05 level: periSylvian asymmetry x EA for tones, periSylvian asymmetry x delta coherence, and resting qEEG asymmetry x qEEG HA for tones. We will discuss the details of each of these combinations in turn.

(1) PeriSylvian asymmetry and delta coherence.

This relation was entirely unexpected. Previous observations had suggested such a relation between periSylvian asymmetry and resting qEEG beta-band power asymmetry (see below), but delta coherence had not been previously examined. The positive sign of the correlation cited in Table IV between periSylvian asymmetry and delta coherence is a simple reflection of the arbitrary way the two variables were coded in these data: periSylvian asymmetry as ranging from extreme positive (RHA) to extreme negative (LHA), while delta coherence was coded as ranging from high to low, with all values coded as positive. Thus high coherence values received codes similar to those for large periSylvian RHAs, and low coherence values were coded similar to small

periSylvian RHAs. An opposite coding would simply have reversed the sign of the correlation without affecting its size or significance.

Table IV. Results of discriminant analysis of 12 subjects tested on 10 variables

variable combination	correlation coefficient	p-value	interpretation
1. periSylvian HA x delta coherence			
POOLED	+.731	.016*	periSylvian RHA
pRfR	+.986	.014*	= high delta
pRfL	+.847	.070	coherence
pLfL	-.991	.083	
2. resting qEEG HA x tones qEEG HA			
POOLED	-.652	.041*	resting qEEG LHA
pRfR	+.560	.439	= tones qEEG RHA
pRfL	-.898	.038*	
pLfL	-.747	.463	
3. periSylvian x EA tones			
POOLED	+.651	.042*	
pRfR	+.163	.837	periSylvian RHA
pRfL	+.897	.039*	= tones LEA
pLfL	+.910	.272	

Given this coding scheme, the positive correlation between periSylvian HA and delta coherence shown for the pooled data ($r = +.731$, $p = .016$) indicates that in brains with a large periSylvian RHA, delta coherence comparing auditory cortex on both sides (T3/4) will be quite high (in our data, approximately 28% or greater). From subject to subject, as the periSylvian asymmetry favors the right-hemisphere less and less, and as it comes to favor the left hemisphere, coherence will systematically diminish. This comparison of the two variables is presented graphically in Fig. C1. Individual subjects provide examples of the extremes, ranging from JL (delta coherence of 35.3% matched with a periSylvian 40 RHA), to MG (delta coherence of 7.4% matched with a periSylvian 130 LHA).

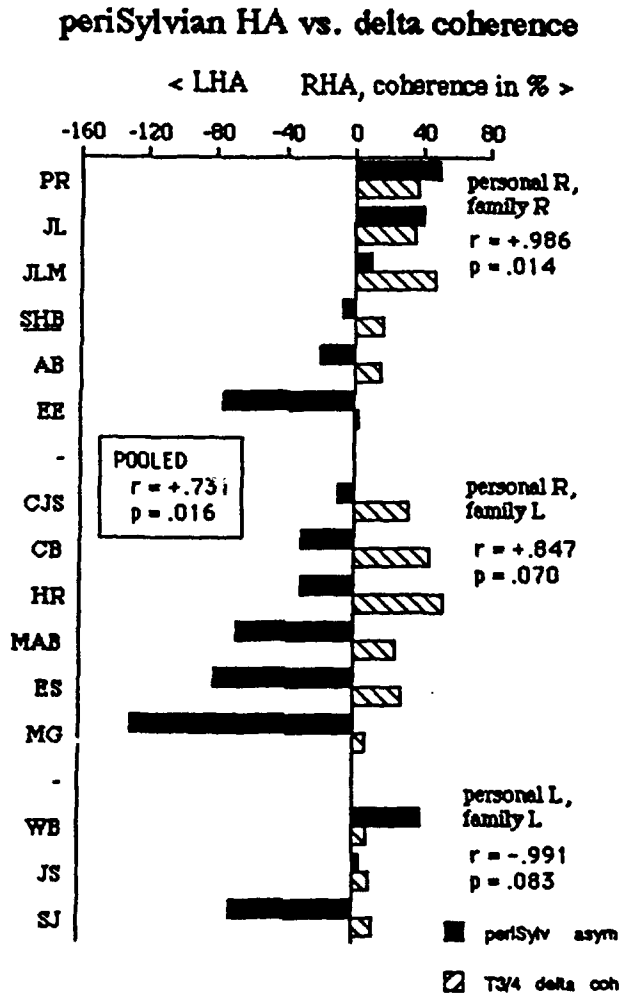


Figure C1. Combined values for periSylvian asymmetry and T3/4 delta coherence (measured during the initial resting condition of each subject's qEEG session). Individuals' data are arranged according to sidedness groups. Discriminant analysis indicated a significant correlation between these two measures in this set of subjects.

As indicated in Table IV, this particular variable combination is significantly correlated only for the pooled data ($p = .016$) and for the pRfR group of subjects ($p = .014$). However, the pRfL subjects also a have high positive correlation ($r = +.847$), which might have reached significance with more subjects. The very high negative correlation for the pLfL subjects is difficult to interpret given the small size of this group and their diversity in terms of periSylvian asymmetry.

There are a number of observations to be made about these very interesting correlations. First, the way the relation is expressed in the three sidedness groups suggests some general rules related to sidedness, as expressed in Table I; these will obviously serve as hypotheses for future testing of individuals from each of these (and other) sidedness groups. Second, the strength of the periSylvian HA x delta coherence relation across all sidedness groups suggests that a re-grouping of the subjects according to periSylvian HA rather than in terms of sidedness may be helpful in future comparisons. Figure C2 illustrates such a grouping -- note the graded change in periSylvian asymmetry from RHA at the top to LHA at the bottom, which is accompanied by graded changes in delta coherence.

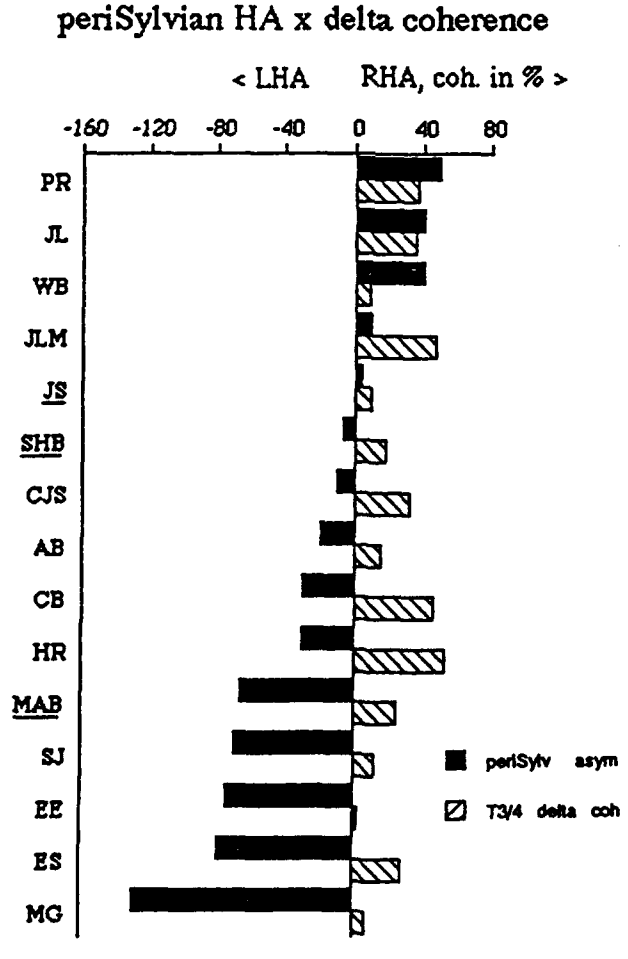


Figure C2. Re-arrangement of the data shown in Fig. C1, according to periSylvian asymmetry rather than sidedness group.

Finally, consideration of the actual magnitudes involved suggests that a categorical analysis of the relation between these two variables may aid in formulating an even more general rule than those defined in Table IV. Such a general rule might transcend sidedness groups, and may also serve as a hypothesis for further testing. The candidate categories are shown defined graphically in Fig. C3, and the data from Fig. C3 are replotted with both periSylvian asymmetry and delta coherence represented as categories, in Fig. C4. The assignment to categories is as follows:

	original range value	new code
PERISYLVIAN		
	all RHAs	+40
	LHAs < 6	-20
	LHAs between 6 and 12	-40
	LHAs > 12	-60
DELTA COHERENCE		
	all values > 28%	+40
	all values between 14 and 28%	-20
	all values < 14%	-40

The match shown in Fig. C4 between these categories of periSylvian asymmetry and the categories of delta coherence point up the way in which this relation holds across sidedness groups, since representatives from different sidedness groups are intermixed from top to bottom according to this ordering. The format of Fig. C4 also serves to highlight departures from this rule, in data from five individuals: WB and JS (coherence "too low" given their periSylvian asymmetry), and CJS, CB, and HR (coherence "too high").

Salient characteristics of these five individuals which may be important in this departure from our hypothetical rule are: 1) both WB and JS are personally left-handed, with left-handed fathers -- the last characteristic distinguishes them from subject SJ, who is also personally left-handed, but with a right-handed father; and 2) all three of the "too-high coherence" subjects (CJS, CB, HR) reported a history of substance abuse, specifically addiction to cigarettes. A within-subject study of HR which was pursued for another purpose, in which ABR stability and qEEG coherence were measured during periods on and off cigarettes (see Appendix D), suggests that the "too-high coherence" in all three of these individuals may be directly related to a pre-existing neurological condition which they are effectively "self-medicating" by means of cigarettes.

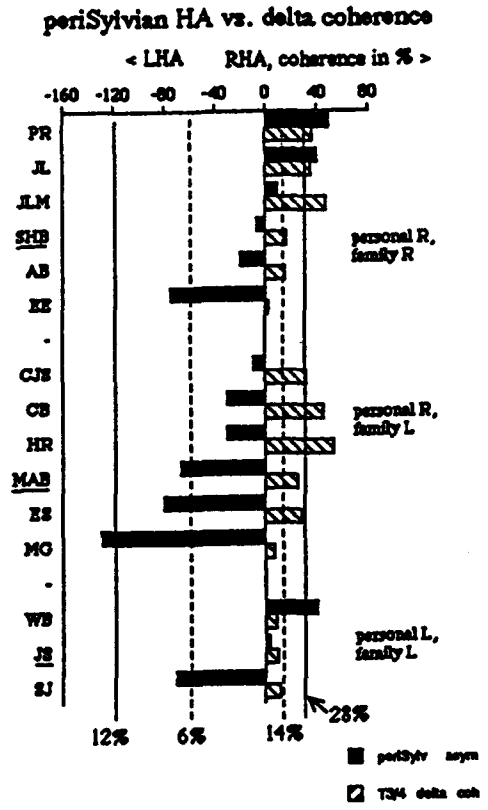


Figure C3. The data from Fig. C2 with suggested "categories" indicated for both periSylvian HA and delta coherence measures (see text for details).

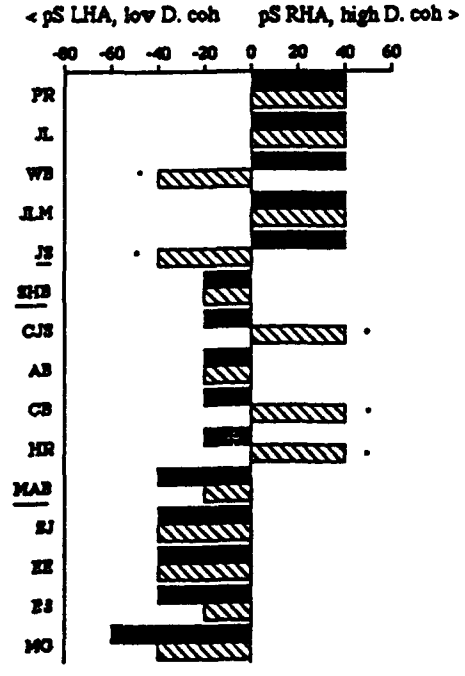


Figure C4. PeriSylvian and delta coherence data replotted in terms of the categories defined in Fig. C3 and in the text. Data points marked with asterisks indicate subjects with "paradoxical" combinations of periSylvian x delta coherence categories, suggestive in some cases of subtle underlying pathology.

These "exceptions to the rule," where the rule is the one posited by the format of Fig. C4, may in fact "prove" the rule: i.e., only in the presence of a crucial "reason" (such as personal left-handedness combined with a left-handed father, or a neurological condition "treated" with substance abuse -- of course, all the features associated with departures remain to be identified) will a subject depart from the rule we can might call the "periSylvian HA vs. delta coherence rule," which states most generally that:

1. a periSylvian RHA predicts that the resting qEEG delta coherence measured at T3/4 will be 28% or higher;
2. a periSylvian LHA predicts that the resting qEEG delta coherence measured at T3/4 will be lower than 28%.

Additionally, there may be gradations within point #2, relating different degrees of periSylvian LHA to different levels of T3/4 delta coherence, as suggested in Fig. C4.

The association of higher T3/4 delta coherence with proportionately greater mass of right-hemisphere auditory cortex has to our knowledge not been noted before. However, this observation may be consistent with other characteristics of the right hemisphere, such as its posited role as a cortical intermediary of "pacemaker" input from subcortical centers. It is also supported by clinical observations, e.g., in addicted individuals, in which knowledge regarding the "predicted level of coherence" (based on the direction and magnitude of anatomical asymmetry) aids in interpreting an interaction between cortical coherence and the physiological characteristics of subcortical structures (see Appendix D, second report).

(2) resting qEEG asymmetry vs. tone-pattern HAs. As indicated in Table IV, the results of the discriminant analysis indicated a significant negative correlation ($r = -.652$, $p = .041$) relating resting qEEG asymmetry (i.e., comparing beta power at T3/4) and the hemisphere advantage evoked during left-ear attention to dichotic tone patterns. The relation is presented graphically in Fig. C5, in which subjects are arranged by handedness group. As is apparent from the group and individual values, the pooled negative correlation depends heavily on data from a very few subjects with extreme scores, and so may not be a fair representation of a general rule.

There are some patterns in this figure, however, which are suggestive. Within the pRfR group (top of the graph), 5/6 have a positive correlation: the qEEG HA for the tone patterns is in the same direction as for the resting asymmetry. Most of the members of the pRfL group have very small HAs either for resting or tone-activated qEEG; the exceptions are ES and MG (who we may remember had the largest periSylvian LHAs of this group). Finally, the pLfL subjects show

their typical diversity of results.

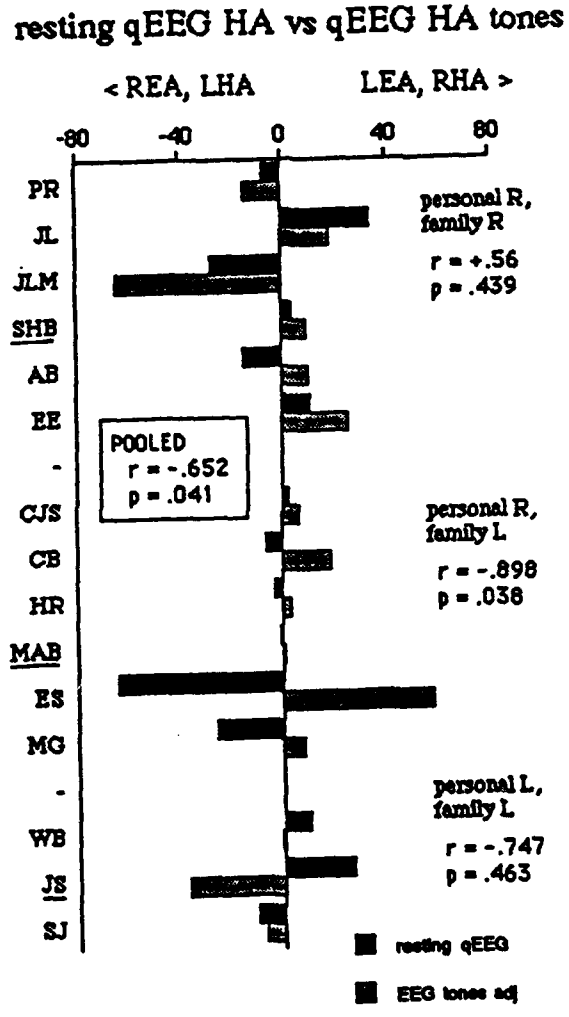


Figure C5. Combined results, arranged by subject sidedness category, for resting qEEG hemisphere asymmetry (beta power asymmetry comparing T3/4) and the qEEG asymmetry observed during left-ear attention to dichotic tone patterns.

The observation about periSylvian values for ES and MG suggest that we should rearrange these results according to periSylvian HA, as in Fig. C6, where the two qEEG measures are combined with periSylvian HAs. The superimposed boxes grouped the normal subjects (regardless of handedness) into three classes: those with periSylvian RHAs (top-most box), those with periSylvian LHAs smaller than 6% (middle), and those with periSylvian LHAs larger than 6% (lower group). Given this division, a pattern of results can be seen within each set of subjects, according to which the periSylvian HA represents the extreme of the three scores, the tone-activation HA represents the other extreme, and the resting qEEG asymmetry provides a bridge between the other two. For subjects in the top box, this takes the form of periSylvian RHAs, associated with resting qEEG asymmetries that are "to the left of this" (whether RHAs as in JL and WB, or LHAs as in PR and JLM), and tone-activation qEEG asymmetries that are still yet further "to the left" (whether still RHA, as for JL, or LHA, as for the other 3 subjects).

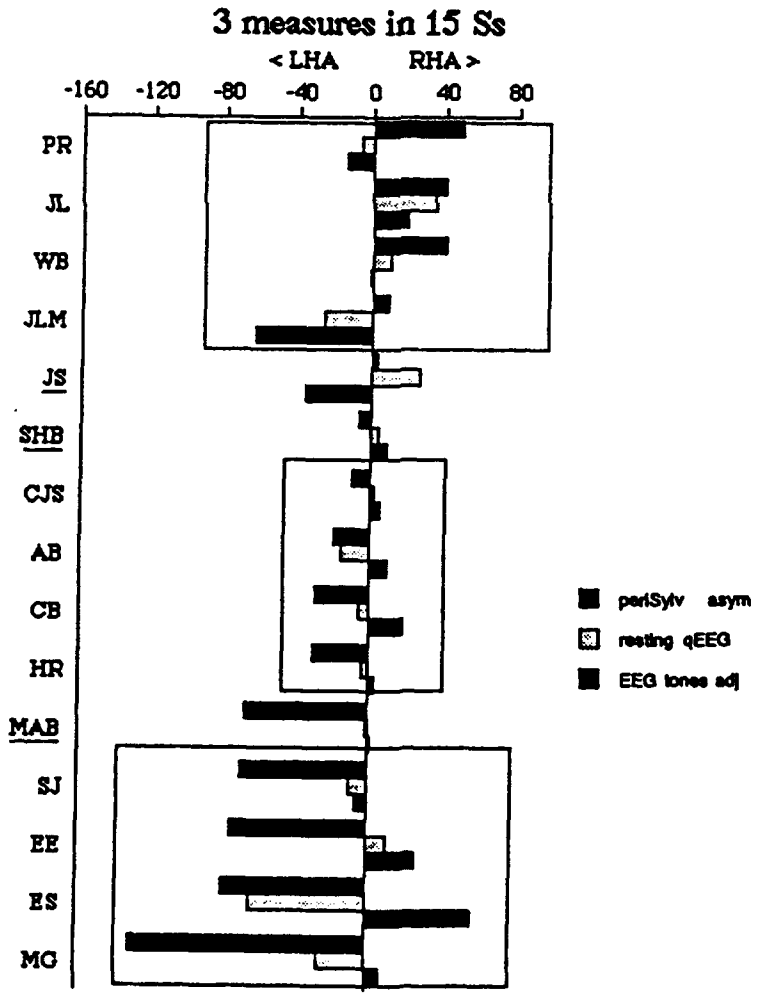


Figure C6. Combination of resting qEEG HA, tone-pattern HA, and periSylvian HA, with data ordered in terms of increasing periSylvian LHA.

For all the normal subjects with periSylvian LHAs, the same pattern holds -- but in a reverse direction: the leftward extreme score is now the periSylvian LHA, with the resting qEEG asymmetry next "to the right," followed by the tone-activation HA most to the right. Note also that the largest resting qEEG asymmetries occur in those subjects with the largest periSylvian LHAs (and in the same direction).

Based on such comparisons, we might hypothesize that given the periSylvian asymmetry and resting qEEG asymmetry, one could predict the direction and estimate the magnitude of the adjusted qEEG HA that would be evoked during left-ear attention to these particular tone patterns. (There are no such patterns which might predict the qEEG HAs for the syllables.) If this proves to be true with further testing, it would be extremely useful information, perhaps precluding the necessity of the time-consuming activation testing, at least for tone patterns. Even less information would be required for those subjects with periSylvian LHAs, since in our data, all of these individuals (middle and lower boxes) have tone-pattern RHAs -- with the single exception of subject SJ, who differs from all of the others in coming from an exclusively left-handed-female family.

(3) PeriSylvian HA vs. tone-pattern EA. As indicated in Table IV, the third relation found to be significant by the discriminant analysis spanned perhaps the widest gap in these data: from anatomy to behavior: periSylvian HA and tone-pattern EA were found to be significantly positively correlated ($r = +.651$, $p = .042$. As the left panel of Fig. C7 illustrates, the high positive correlation is strongest in the two groups from left-handed families (subjects without behavioral results for the tone patterns are marked with asterisks). Arranging subjects according to periSylvian HA (right panel) shows that the relation is very specific with regard to direction and magnitude of periSylvian HA. First, in all subjects with either a periSylvian RHA or a small periSylvian LHA (less than 6%), the tone patterns evoked a left ear advantage. Second, of the 5 subjects with large periSylvian LHAs (> 6%), 3 had REAs for the tone patterns, while 2 (EE and ES) had LEAs. It might be noted that these last two subjects were also distinctive among the large-LHA group in having large RHAs for the tone patterns during qEEG testing (cf. Fig. C6). Whatever accounts for this pattern is not clear, but at least the behavioral vs. qEEG tone-activation findings in these two individuals is strikingly consistent.

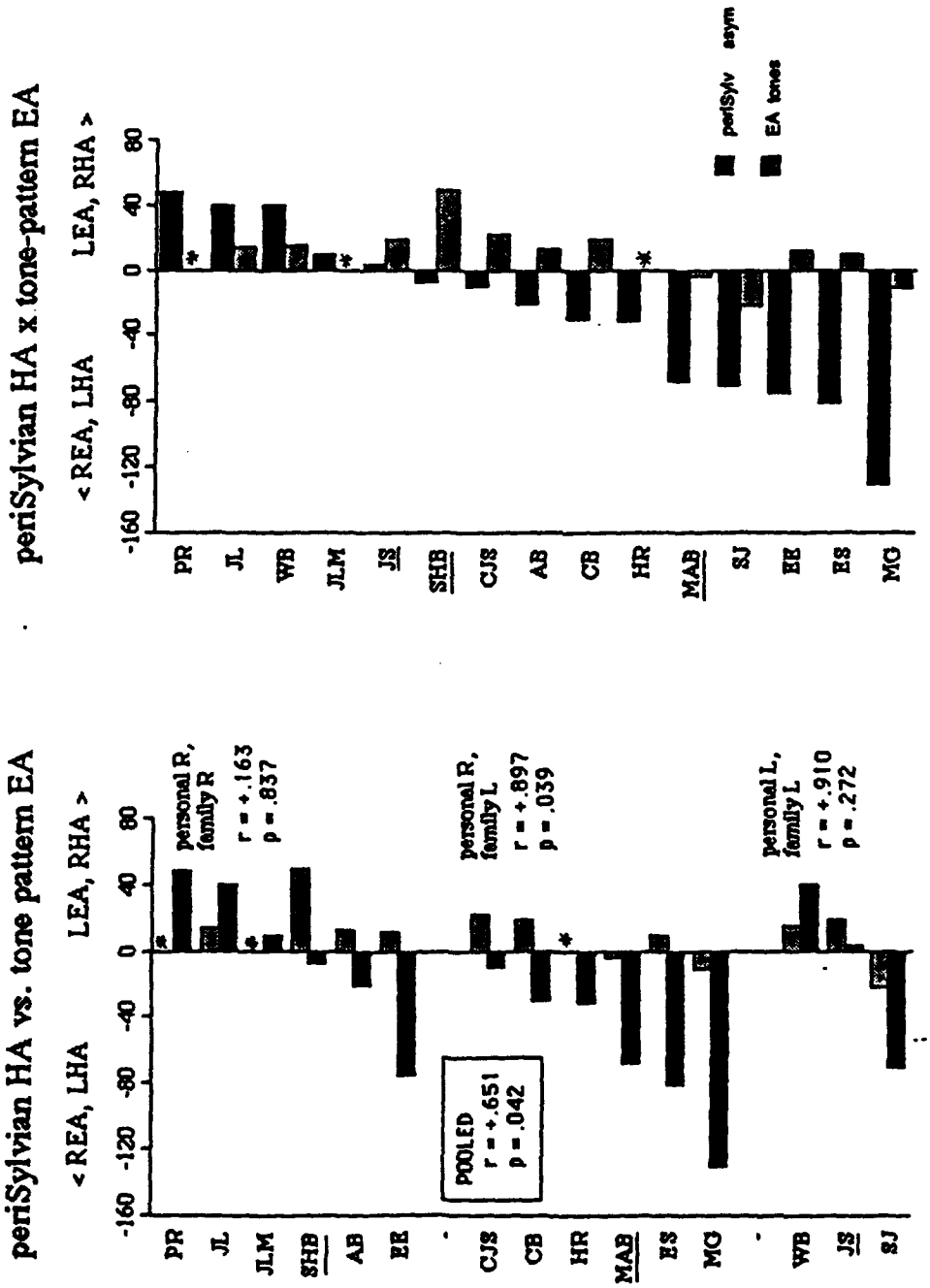


Figure C7. Combined data for periSylvian HA and the ear advantage measured during behavioral testing for the tone patterns, arranged according to subject sidedness group (left panel) and according to periSylvian HA (right panel).

Putting this result (periSylvian x tone EAs) together with the preceding one (periSylvian x tone qEEG HAs), then, one might be able to formulate rules for predicting both the behavioral EA as well as the qEEG HA evoked for these particular tone patterns, based only on information regarding the periSylvian asymmetry:

1) a periSylvian RHA predicts a behavioral LEA for the tones (Fig. C7); in order to predict the qEEG HA for the tone patterns in these subjects, one must add information about the resting qEEG asymmetry (beta power difference over T3/4).

2) a periSylvian LHA predicts a qEEG RHA for the tones, unless the subject is from an exclusively female-left-handed family (Fig. C6); and it predicts two outcomes for the behavioral score, according to the size of the periSylvian asymmetry: LEA if the periSylvian LHA is smaller than 6%, and REA if the periSylvian LHA is larger than 6% (Fig. C7).

(4) Additional considerations. While there are a myriad other variable combinations in these data which could be examined, these are the only three which were judged to be significantly correlated by the discriminant analysis. However, as we have seen, this type of analysis is not sensitive to all of the information in the data, such as patterns involving more than two measures, or accounting for other unquantified characteristics of the subjects, such as a history of substance abuse.

It is specifically with regard to this last characteristic that we would like to conclude this discussion by considering two additional variables which did not enter into significant correlations according to the discriminant analysis, namely, the data derived from the auditory brainstem response (ABR) test given to each subject. It was originally hoped that this examination of the subcortical portion of the auditory system would provide a useful complement to the other measures, most of which were considered to focus on the auditory cortex.

The data points taken from the ABR test for each subject are shown in Fig. C8. In the left panel are displayed values representing the percent difference in absolute amplitude of peak III comparing left- and right-ear stimulation conditions. This value was selected based on previous authors' suggestions that this brainstem "ear difference" might be an important index of overall auditory-system function (Levine & McGaffigan 1983). As shown in this panel, there is a clear relation between periSylvian asymmetry and the ear "favored" in this way in the brainstem response: normal subjects with a periSylvian RHA have a brainstem LEA, while those with a periSylvian LHA have a brainstem REA. Both of these patterns are "contralaterally consistent," i.e., that hemisphere with the larger auditory cortex favors input from the contralateral ear peripherally.

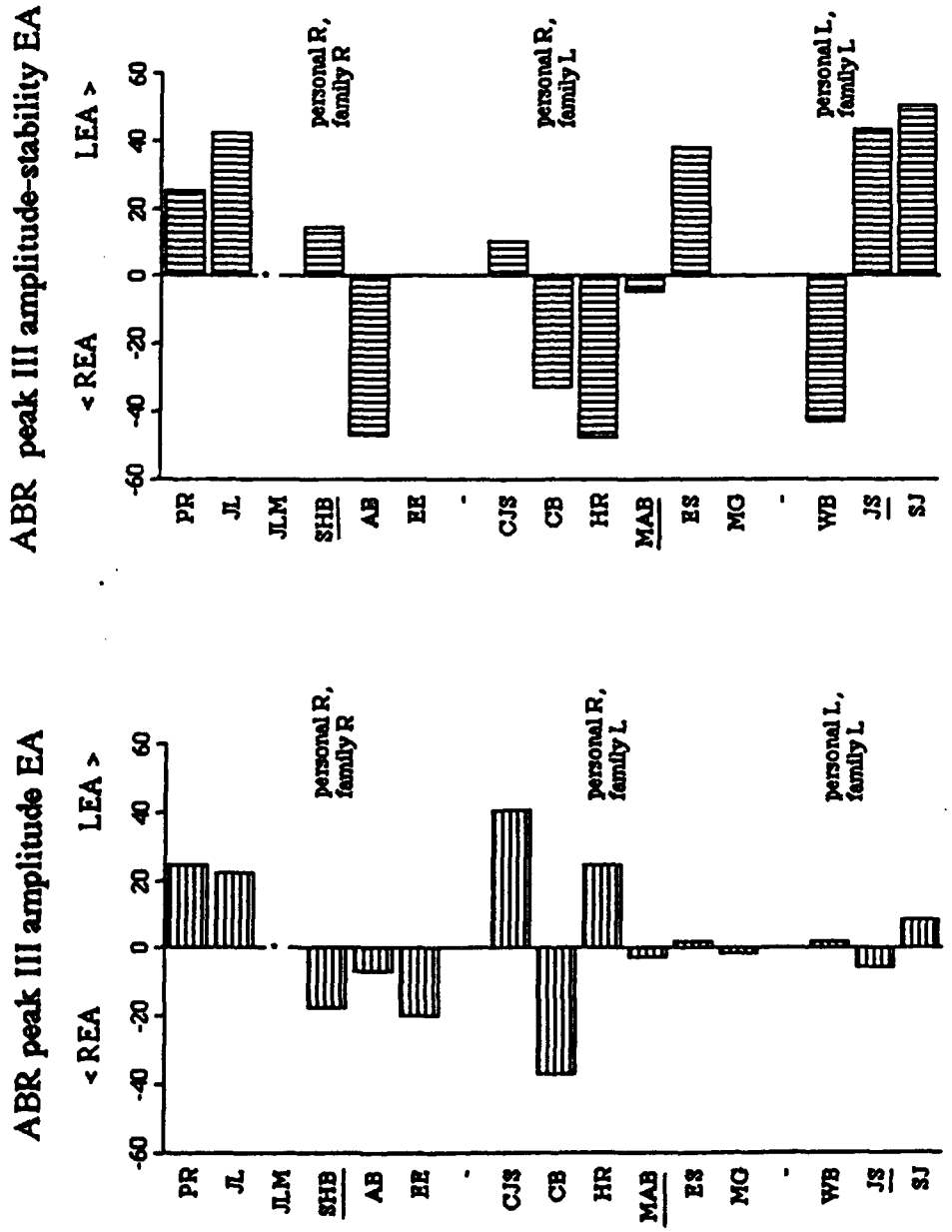


Figure C8. Two measures of asymmetry taken from the Auditory Brainstem Responses (ABRs) collected in these 15 subjects. Each represents an "ear difference" based on percent-difference comparison of ABR peak III amplitude characteristics observed during left-ear vs. right-ear stimulation conditions: ear difference based on ABR peak III mean amplitude (left panel); and ABR peak III amplitude stability (right panel).

Exceptions are CJS and HR (two of the three subjects we have noted have a history of substance abuse), and SJ (the one subject here from an exclusively female-left-handed family). As discussed in Appendix D, the relation between auditory function at the level of the brainstem vs. at the level of the cortex may be extremely important as a diagnostic sign if not as a clue to etiology in some subjects who report a history of substance addiction.

In the right panel of Fig. C8, the data for the ear difference in the stability of this same measure is plotted, based on calculations used in our REPs/ABR procedure (see Appendix D for more details). These values represent the mean divided by the standard deviation of the amplitudes used to calculate the simple ear difference plotted in the left panel of this figure. The figure shows that the amplitude-stability EA displays a somewhat more complex pattern of values for the different subjects, but one which seems to be equally systematic.

First, for the normal individuals with periSylvian RHAs and those with very small periSylvian LHAs (< 1%), ABR peak III amplitude stability favors the left ear. In subjects with a moderate periSylvian LHA (between 1% and 6%), amplitude stability will favor the right ear. Subjects with large periSylvian LHAs (> 6%) seem to be unique among these individuals in showing little or no amplitude-stability EA (MAB, EE, MG). The exceptions to both of these rules are three women, one of which (SJ) is from an exclusively female-left-handed family, and the other two of which are related: WB is the left-handed daughter of right-handed ES. It is possible that this test is the only one of this battery which is sensitive to ES's reported tendency to be as much ambidexterous as right-handed, and that the exceptions shown on this graph are all instances of females coming from female-left-handed families.

Clearly many more subjects representing all of the different groups described above must be tested with this or a similar battery before we will be able to resolve the nature of the patterns and exceptions noted here. Not only are members of a variety of sidedness groups needed, but subgroups controlling for other features such as a history of addiction and hyperactivity should be included within each of the sidedness categories. The sensitivity of these tests to subtle individual characteristics such as a tendency to compulsive behavior validates their ability to provide new information about subtle neurological distinctions among individuals who would otherwise be classified as "normal."

Of course, it is just this sensitivity, both of individual tests and most particularly of their coordinated combination in batteries such as used for the CNS Project, that promises new insights into human neuroscience. Not only can we expect to learn more in this way about the specific problems of pathological individuals (such as JS, SHB, and MAB included here), but also to acquire a more

sophisticated appreciation of the "range of normality," which should guide us to a new understanding of the relations between human brain anatomy, physiology, and behavior, with implications for dealing with normal as well as neurologically disordered individuals.

IV. Individual Profiles

The focus of this research is not on population characteristics, but on individuals. Under the view of this Project, populations are only to be defined in a "bottom-up" way by the characteristics of individuals comprising them, and as indicated in the previous section, it is probable that the more we know about individuals, the more our notions about what characterizes a population will change. Indeed, one goal of the research is to demonstrate the serious shortcomings of a priori grouping of subjects, and illustrate that the only way to discover what groups exist in terms of brain organization is to obtain as much information as possible on each individual subject. Thus the parameters defining a "group" are only generated by the characteristics of individuals -- one cannot ignore one feature of an individual in order to fit her/him into a pre-defined group defined according to a different feature -- and it is entirely to be expected that the definitions of "groups" will continue to change as more individuals are studied.

Thus an important section of this report is the following, devoted to a more intensive examination of within-subject characteristics, and the tentative first steps toward exploring how these individual characteristics themselves gather individuals into groups of two or more. It should not be assumed that every brain is built in the same way, or works in the same way, or that behavior in every individual is the same (even on highly controlled laboratory tests), but parsimoniously, neither should we assume that every individual is a law unto her/himself. Grouping subjects in a "bottom-up" way, making use of multiple observations of each subject, with no a priori assumptions about group definitions, should eventually lead to a formulation of the "repertoire" of ways in which brain organization accomplishes behavior.

The multiple panels of Fig. I1 present the "CNS profiles" of all 15 subjects included in this feasibility study. For the first time in this report, these graphs bring together the various test techniques in the way envisioned in the original proposal, to enable us to examine the degree of "within-subject consistency" of the various measures of auditory-system asymmetry.

Hypotheses regarding the terms of this type of consistency were based on previous thinking about the ways in which measures such as ear advantages were related to the brain, as well as on neurophysiological notions as to how brainstem and cortical levels of the human auditory CNS should interact. Thus, for the tests covered here, the following hypotheses might have been reasonable predictions for a subject who was right-handed from a right-handed family:

1. Dichotic syllables will evoke REA according to behavioral methods, and dichotic syllables with right-ear attention will evoke a (contralateral) LHA measured with qEEG.

2. Dichotic tone patterns of the type tested here will evoke LEA behaviorally, and a (contralateral) RHA when tested under qEEG.

3. Whole-hemisphere asymmetry will be RHA (based on the literature on auditory-cortical asymmetries in pRfR subjects).

4. PeriSylvian asymmetry will be LHA (again, based on that literature).

5. No predictions based on previous literature would have been available for either the resting qEEG measures (T3/4 beta power asymmetry, and delta coherence) or the brainstem measures (peak III amplitude EA, and amplitude-stability EA). However, two estimated outcomes might have been made:

a. Assuming a greater tissue mass would generate greater electrophysiological activity than a lesser one, one might have predicted that qEEG beta power asymmetry would favor the same side as the periSylvian asymmetry.

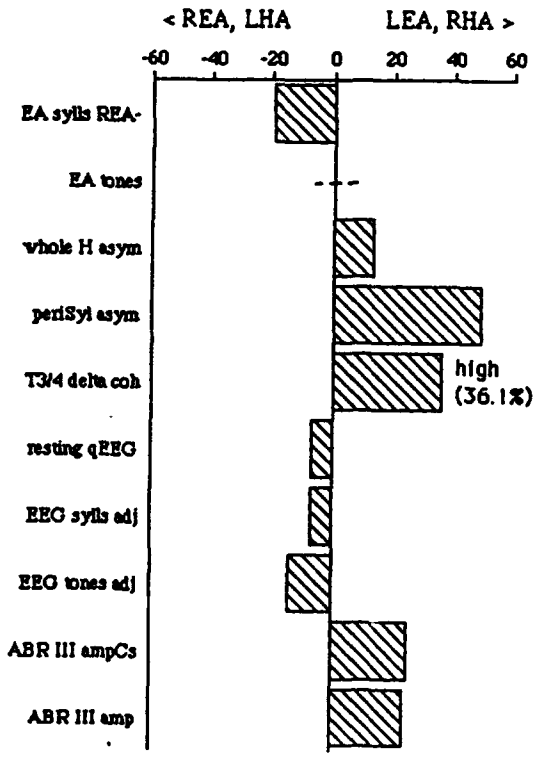
b. Assuming that these two latter measures reflect the contralateral organization of the auditory CNS, one might have predicted that the side thus favored in the cortex would be contralateral to the side favored at the brainstem level, such that ABR peak-III amplitude would be both larger and more stable in response to the contralateral ear.

c. There was no basis for predicting outcome relating delta coherence to the other measures, other than vague intimations in the literature linking "increased hemisphere coordination" with "right-hemisphere activation." In fact, in this report, delta coherence has been added after the fact as a dependent variable, as a result of previous indications of its importance for interpreting the results of a clinical study related to auditory asymmetries (see presentation texts on central auditory disorders included in Appendix E).

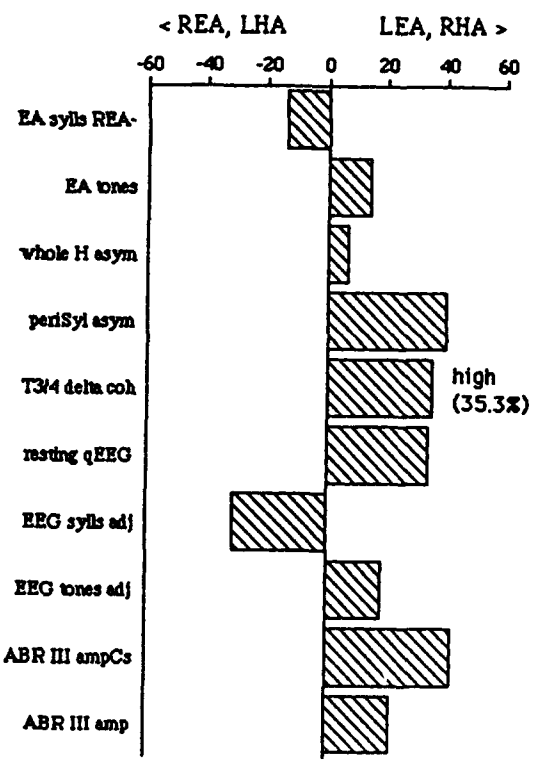
Given these hypotheses and the format of the individual profiles in Fig. I1, one could conclude that a profile confirming all the hypotheses would have a very simple form: only bars representing the dichotic syllables (tested both with behavioral and qEEG methods) would extend toward the left side of the graph, while all other values would be represented by bars extending toward the right. Examination of the profiles in Fig. I1 indicates that only JL's data take this shape.

Of course, the insistence on asymmetry values vis-a-vis the central zero line is a simplistic one: our previous work on asymmetries stresses relative rather than absolute values, and in some cases, the importance of ignoring a quantified "midline." However, in brain measurements where the "midline" is a literal fact, one should probably seek to find ways in which relative asymmetries may be interpreted in terms of the brain's more or less bilateral organization.

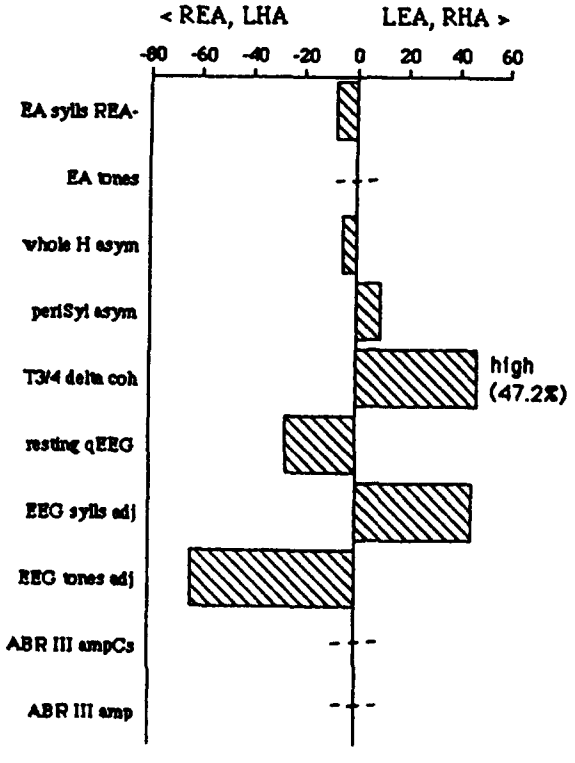
PR (23yr male; personal R, family R)



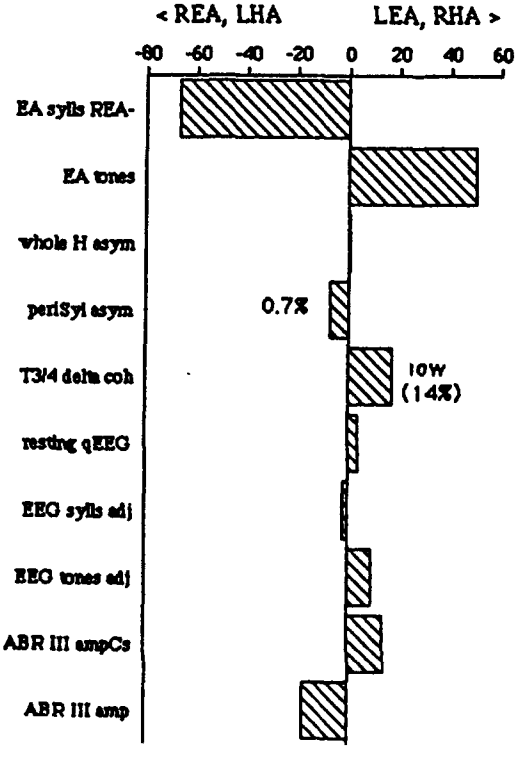
JL (45yr female; personal R, family R)



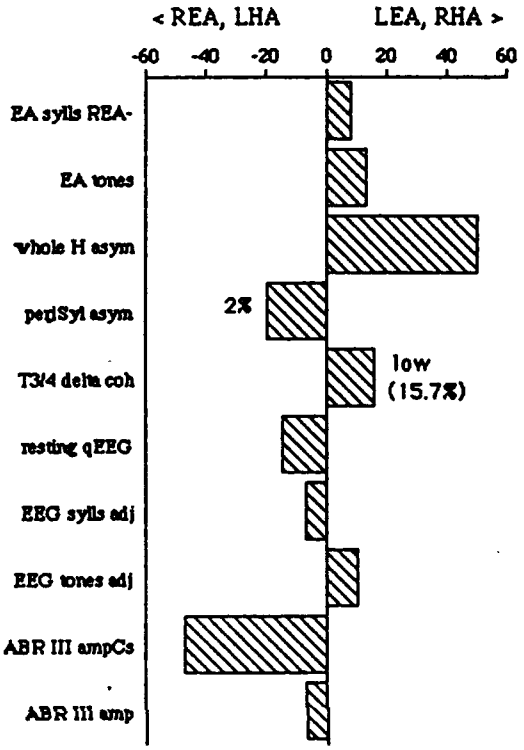
JLM (38yr female; personal R, family R)



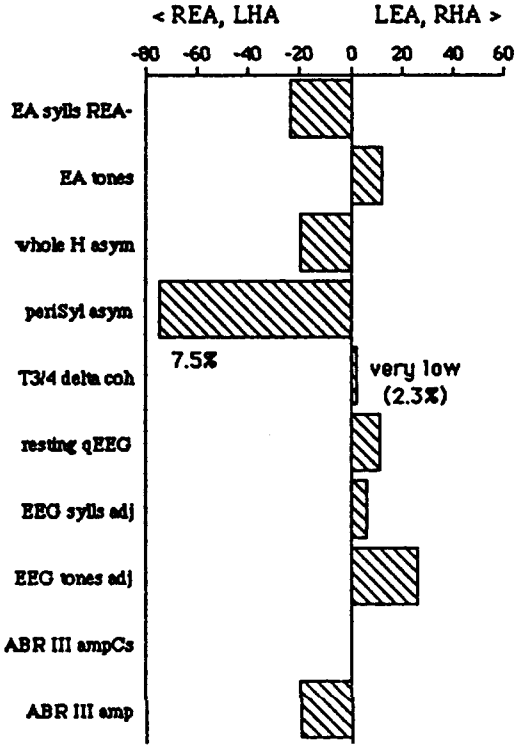
SHB (40yr female; personal R, family R)
CENTRAL AUDITORY DISORDERS



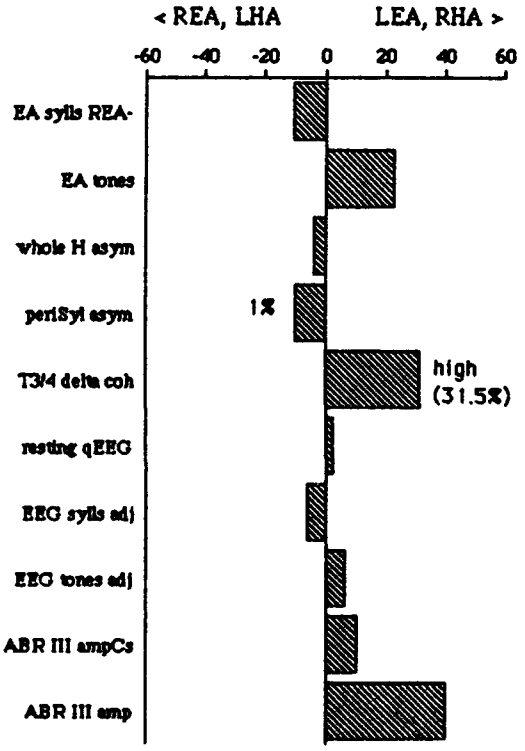
AB (22yr female; personal R, family R)



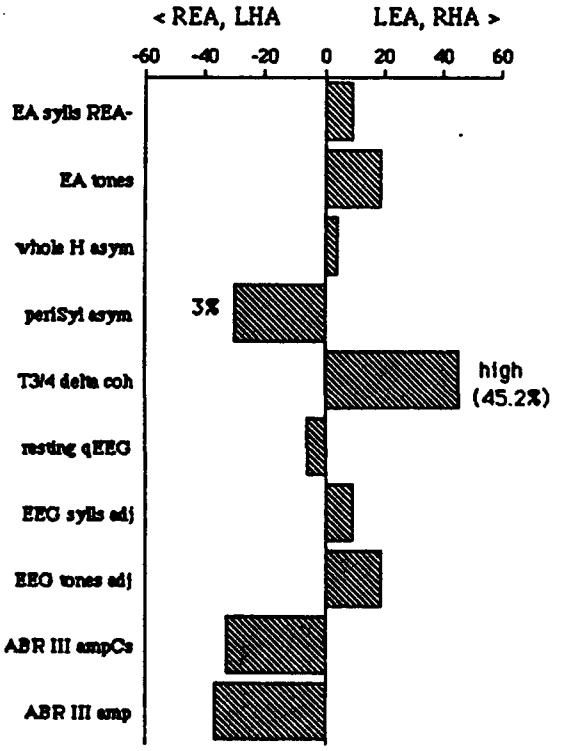
EE (17yr female; personal R, family R)
CHINESE FATHER



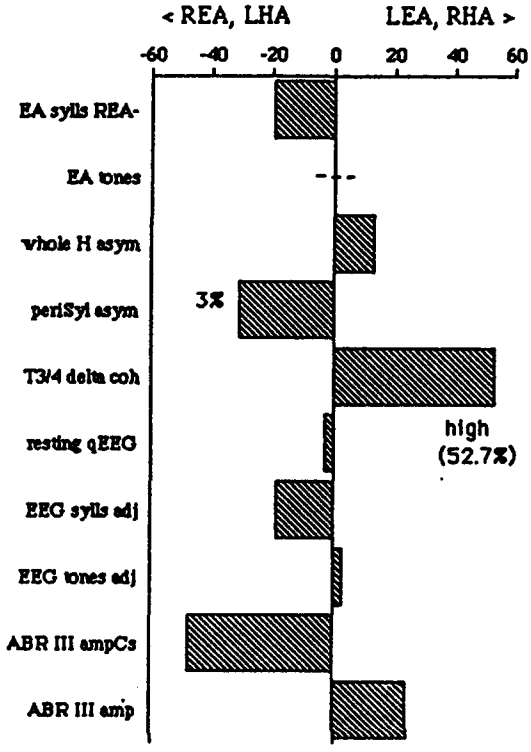
CJS (33yr female; personal R, family L)



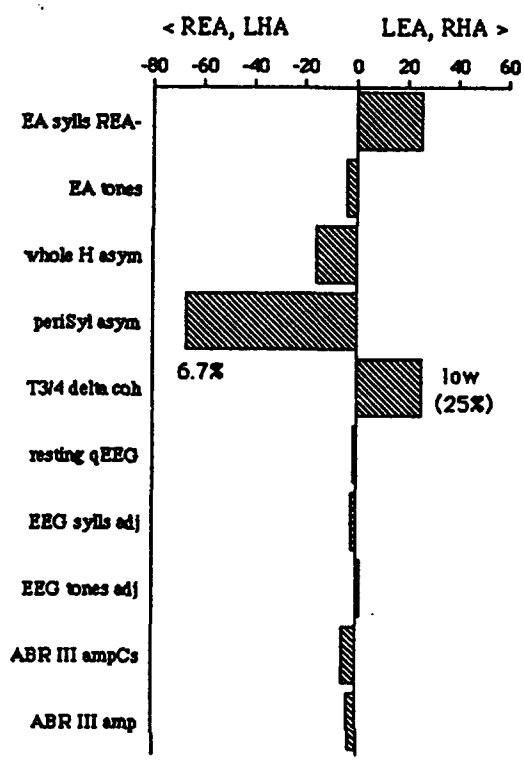
CB (43yr female; personal R, family L)



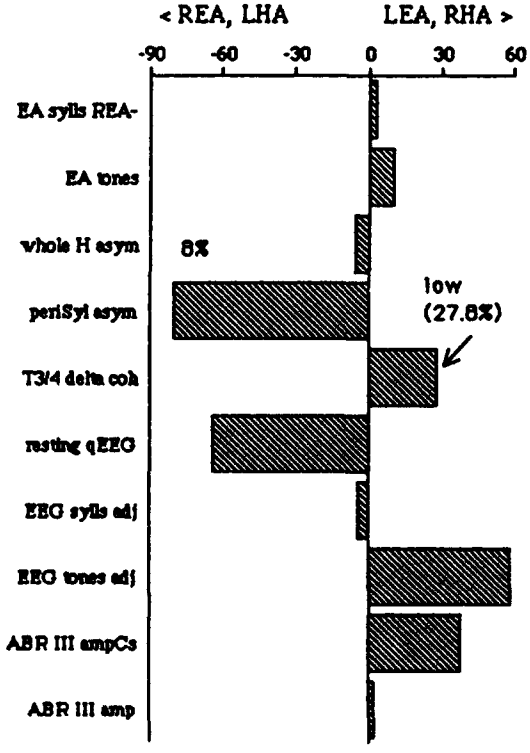
HR (22yr female; personal R, family L)
ADDICTED SMOKER



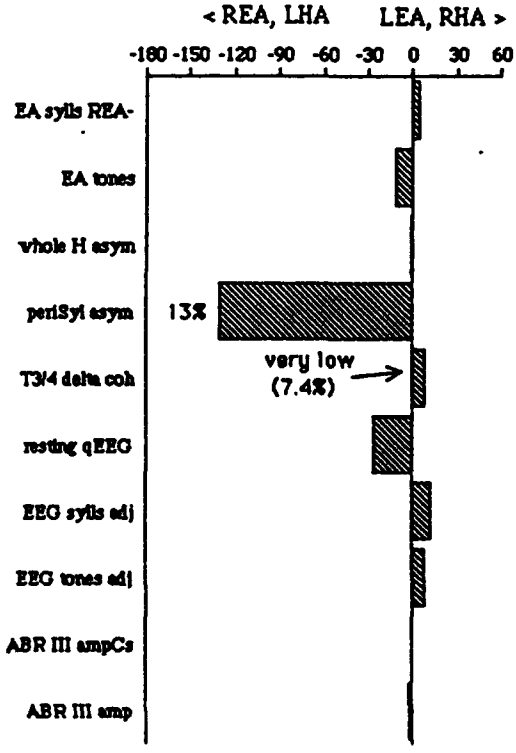
MAB (27yr male; personal R, family L)
CENTRAL AUDITORY DISORDERS

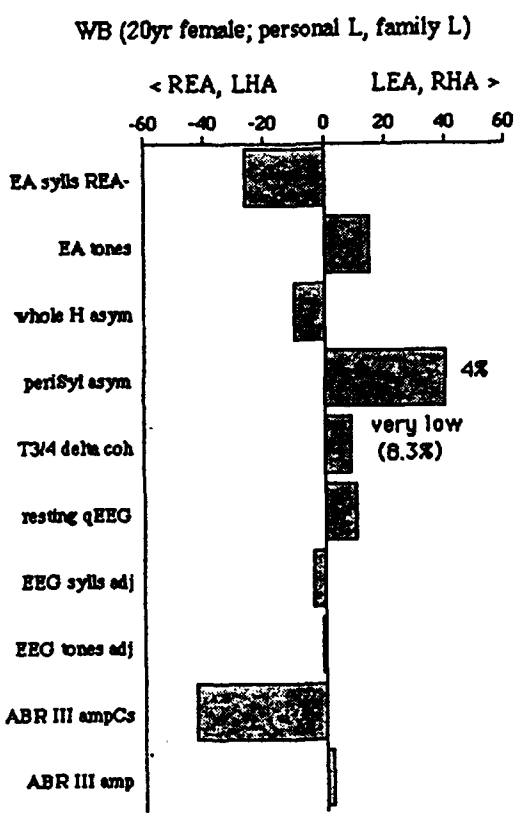


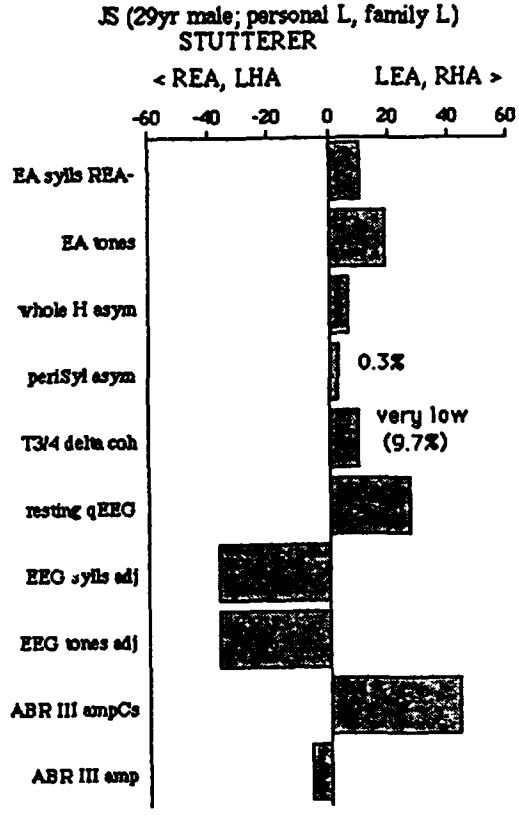
ES (45yr female; personal R, family L)

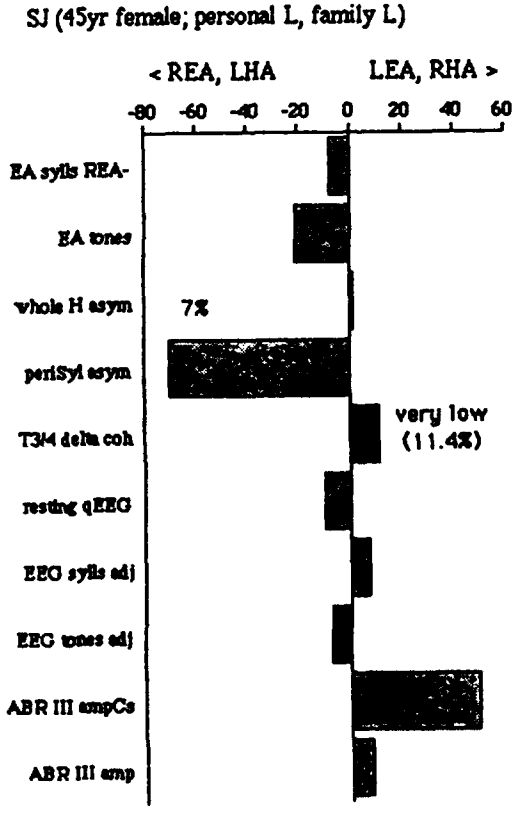


MG (16yr male; personal R, family L)




WB (20yr female; personal L, family L)
< REA, LHA
LEA, RHA >
-60 -40 -20 0 20 40 60
EA sylls REA-
EA tones
whole H asym
periSyl asym
T3/4 delta coh
resting qEEG
EEG sylls adj
EEG tones adj
ABR III ampCs
ABR III amp
4%
very low
(8.3%)


JS (29yr male; personal L, family L)
STUTTERER
< REA, LHA
LEA, RHA >
-60 -40 -20 0 20 40 60
EA sylls REA-
EA tones
whole H asym
periSyl asym
T3/4 delta coh
resting qEEG
EEG sylls adj
EEG tones adj
ABR III ampCs
ABR III amp
0.3%
very low
(9.7%)


SJ (45yr female; personal L, family L)
< REA, LHA
LEA, RHA >
-80 -60 -40 -20 0 20 40 60
EA sylls REA-
EA tones
whole H asym
periSyl asym
T3/4 delta coh
resting qEEG
EEG sylls adj
EEG tones adj
ABR III ampCs
ABR III amp
7%
very low
(11.4%)

One way of approaching the task of interpreting relative asymmetries in terms of bilateral brain organization is to explore ways in which subjects can be grouped on the basis of the pattern rather than the absolute values of the individual measures. For this purpose, a cluster analysis was used with the data, in which results for 12 subjects (omitting the incomplete data sets for PR, JLM, and HR) tested on 10 variables were compared. The hierarchy of cluster formation, together with the pseudo-F and pseudo t^2 values, are presented in Table V.

Table V. Results of cluster analysis of 12 subjects tested on 10 variables.

Cluster members	pseudo F	pseudo t^2
1. EE, MAB	3.37	--
2. AB, CB	3.54	--
3. JL, CJS	3.46	--
4. EE, MAB, SJ	3.49	1.49
5. EE, MAB, SJ, MG	3.62	1.29
6. JL, CJS, JS	3.84	1.32
7. SHB, WB	4.13	--
8. EE, MAB, SJ, MG, ES	4.46	1.94
9. JL, CJS, JS, SHB, WB	5.19	1.82
10. JL, CJS, JS, SHB, WB, AB, CB	6.20	2.83

pseudo *F* measures the separation among all clusters at the current level; pseudo t^2 measures the separation between the two clusters most recently joined

A series of graphic presentations of these clusters, combining the individual profiles of Fig. I1, are presented as Figs. I2-I6. Consideration of these cluster results gives rise to a number of observations.

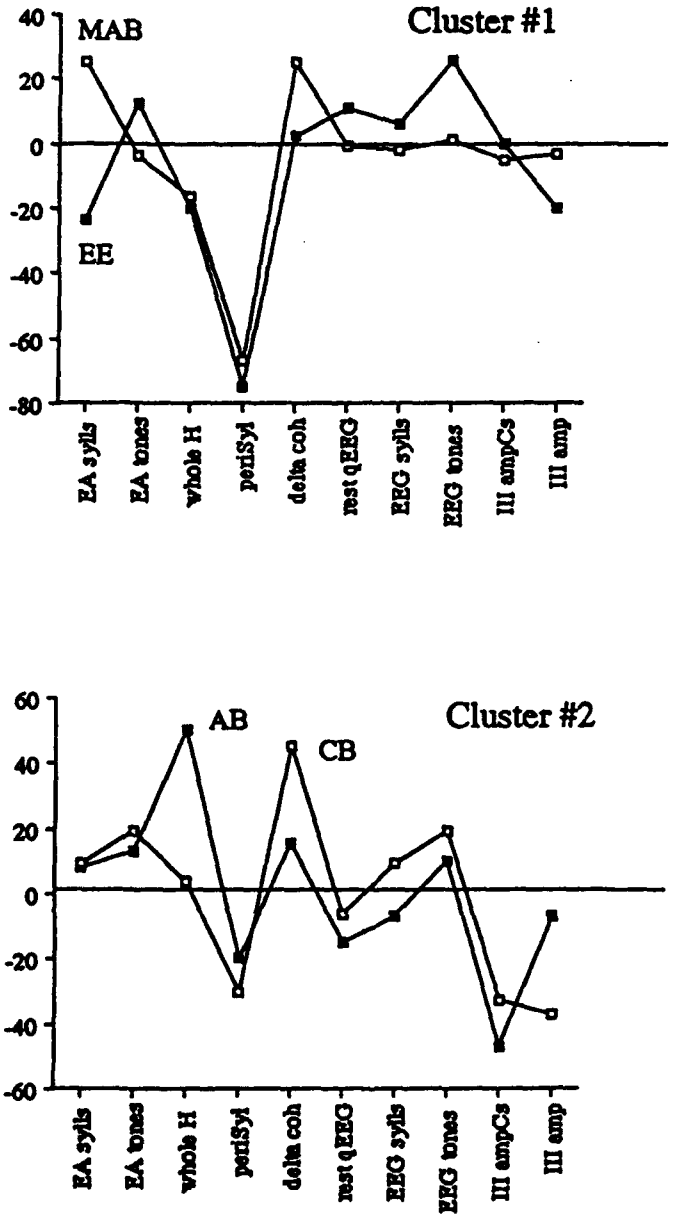


Figure I2. Individual "CNS profiles" for subjects grouped according to the cluster analysis as Cluster #1 (top panel) and Cluster #2 (lower panel).

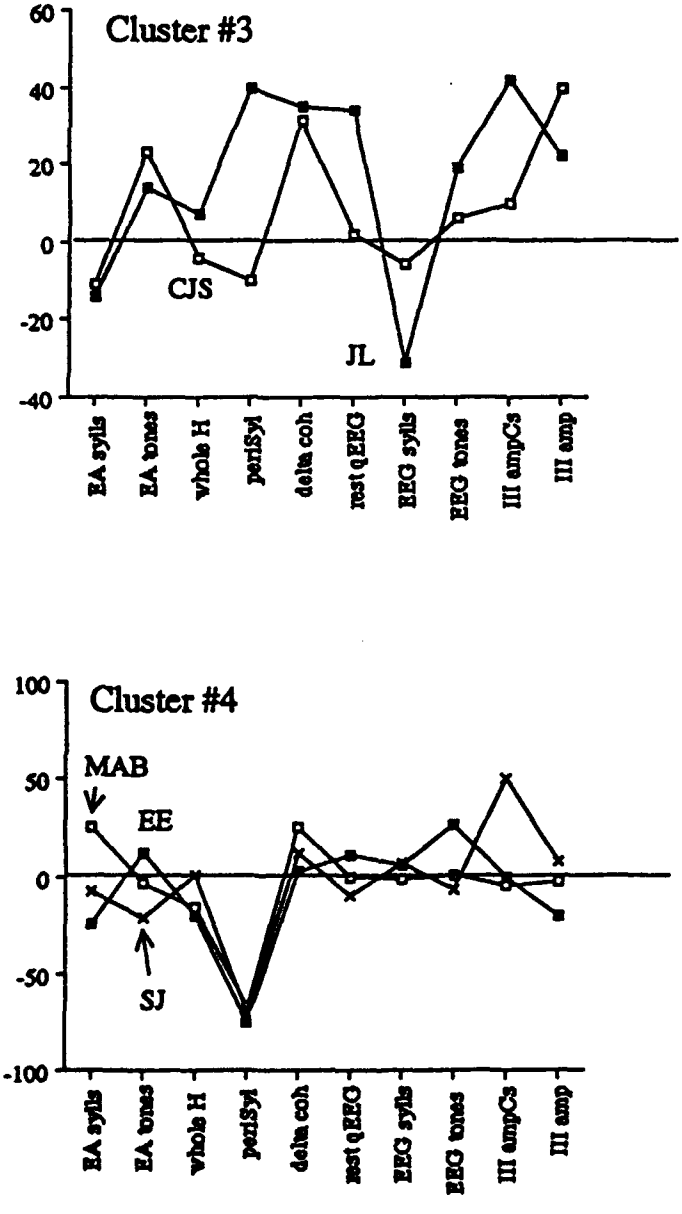


Figure I3. Individual "CNS profiles" for subjects grouped according to the cluster analysis as Cluster #3 (top panel) and Cluster #4 (lower panel).

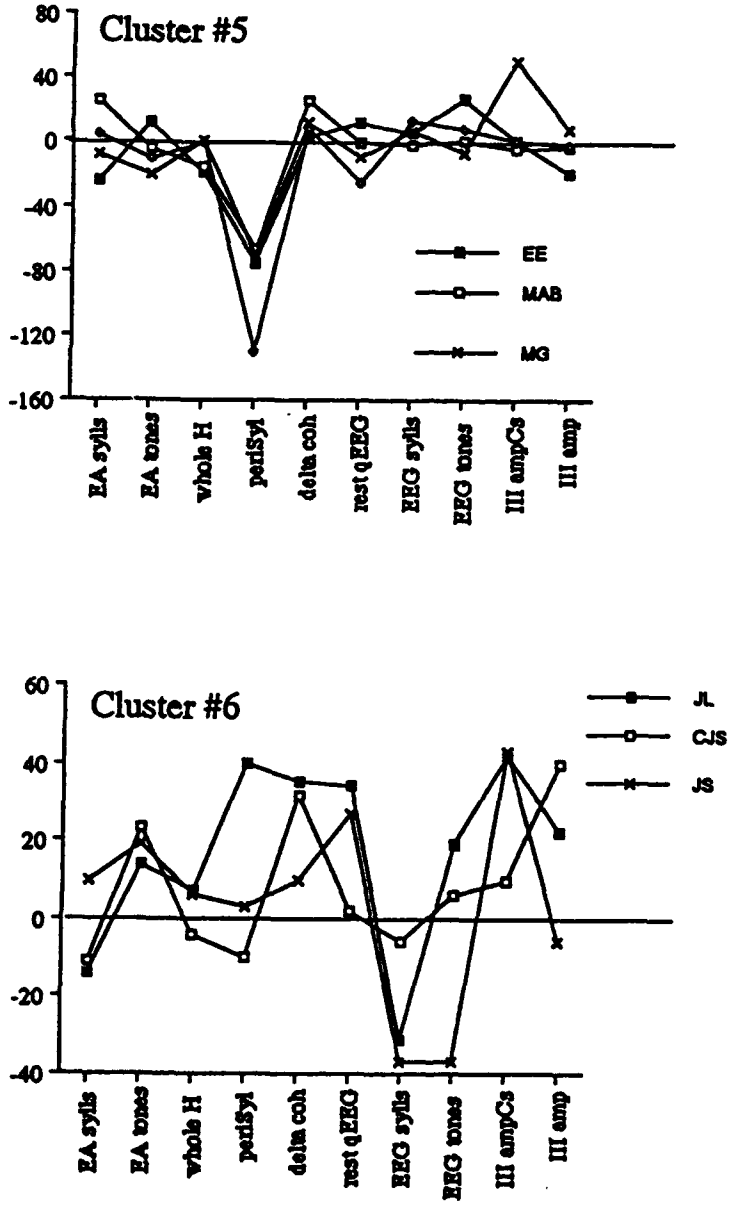


Figure I4. Individual "CNS profiles" for subjects grouped according to the cluster analysis as Cluster #5 (top panel) and Cluster #6 (lower panel).

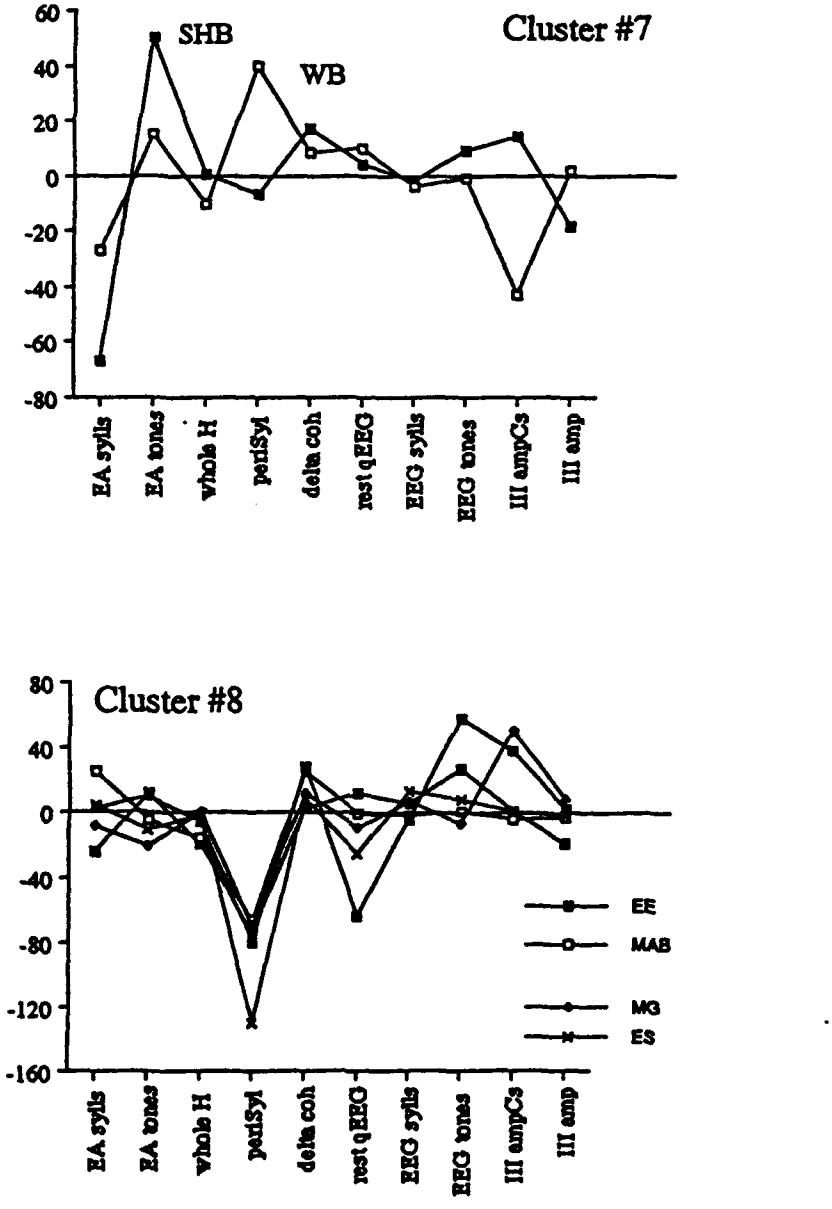


Figure I5. Individual "CNS profiles" for subjects grouped according to the cluster analysis as Cluster #7 (top panel) and Cluster #8 (lower panel).

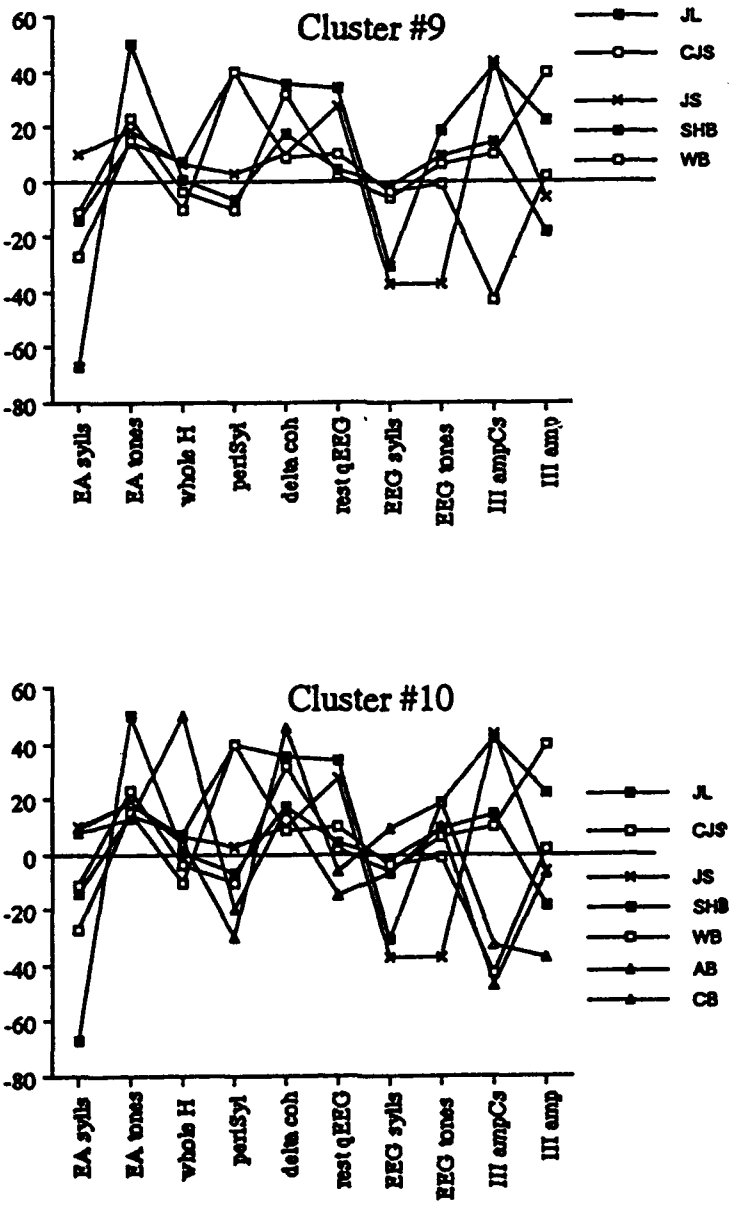


Figure I6. Individual "CNS profiles" for subjects grouped according to the cluster analysis as Cluster #9 (top panel) and Cluster #10 (lower panel).

Cluster #1: In terms of anatomical auditory-system asymmetries, EE and MAB are almost identical, though EE is a high-school woman of 17 years, right handed from a right-handed family, and MAB is a 27-year-old man, right handed with a left-handed father. An interesting sidelight to the makeup of this cluster, which is the "tightest" of all here, is that EE is the only subject with an Oriental family (father), and MAB came to our study with the diagnosis of "central auditory disorder." This observation is one of several findings that have led to an interest in including more detailed comparisons between Oriental and Caucasian populations among future research topics for the CNS Project. It is also of interest that this "tightest" of all the clusters crosses genders.

The "clinical signs" here of MAB's difficulties in fact occur at points where he differs from EE: 1) the reversed ear advantages, and 2) near-zero values for the series of measures starting with resting qEEG. His reversed ear advantages (cf. Table I) were caused by a "drop-out" score in for right-ear attention to dichotic syllables, pointing initially to a left-hemisphere problem. Subsequent testing with REPs/ABR revealed a "release sign" in the response to right-ear clicks, also diagnostic of left-hemisphere pathology, and the lack of a resting qEEG asymmetry in the face of his dramatic periSylvian LHA further corroborated the diagnosis of a dysfunctional left-side auditory cortex. (For complete details of this clinical study, see Appendix E.)

Cluster #2: This cluster represents yet another pair of subjects whose patterns of measures put them together in spite of the fact that they represent two sidedness groups (AB is pRfR, and CB is pRfL). The two functions are strikingly alike, with the two main departures being AB's very large periSylvian LHA (unique in these subjects), and CB's very high delta coherence, which as suggested above may be related to the fact that she has a history of substance abuse.

Cluster #3: Distinctions between these two subjects who are judged to be quite similar by the cluster analysis in spite of their different sidedness group membership (JL = pRfR, CJS = pRfL) can be accounted for by a series of measures which seem to be closely related not only within the dataset for each subject, but also the ways in which the values contrast. First, both JL's periSylvian asymmetry and resting qEEG asymmetry strongly favor the right hemisphere, whereas CJS presents with a small periSylvian LHA, with virtually no resting qEEG asymmetry. In fact, as suggested above, the observation in CJS of a very high delta coherence (similar to JL's) in the face of her paradoxical periSylvian LHA may be related to her history of substance abuse. Finally, the distinctions in these two subjects' ABR stability scores may follow from their differences in resting qEEG asymmetry, representing contrasting but appropriate "contralateral matches" both in terms of direction and magnitude to the value of

the two subjects' contrasting resting qEEG HAs.

Cluster #4: At this point in the analysis, the pattern of results for subject SJ was judged similar enough to that of subjects from Cluster #1 to be joined with them. This is certainly a "strange bedfellows" group: EE (pRfR) with her Chinese father, MAB (pRfL) with his "central auditory" complaints, and SJ (pLfL), the only one of these subjects for whom left-handedness was confined exclusively to the females of her family.

The pattern of "reversed ear advantages" which in MAB was the first clue to his central disorder occurs "normally" in SJ, with her maternally left-handed family. In fact, on all the measures SJ is more like MAB than she is like EE, with the single exception her large LEA in ABR amplitude stability, strangely "ipsilateral" to her small resting qEEG LHA -- for which we have no current explanation, except that all three pLfL subjects have very large ABR amplitude stability EAs in the face of small resting qEEG HAs.

Cluster #5: Adds subject MG to the group from Cluster #4. MG continues the "strange bedfellows" character of this group: he is the only one of these subject with a Mexican-American background, and it is tempting to consider the possible importance of the influence of Oriental gene pools (such as those represented in subject EE) in this ethnic group. His scores are strikingly similar to the others', looking particularly like SJ's, without her large ABR amplitude stability EA.

Cluster #6: Adds subject JS to JL and CJS from Cluster #3. The points according to which JS departs from the other two may be related to his history as a stutterer: 1) his delta coherence is low given the nature of his periSylvian asymmetry (see section above on this relation); 2) his resting qEEG asymmetry is large given the small periSylvian RHA; 3) it is extremely unusual that the qEEG HAs for syllables and tone conditions are identical, and his difference from the other two here suggests that the problem is in the tone HA rather than in the response to syllables); and 4) his ABR amplitude REA is ipsilateral rather than contralateral to the otherwise favored right-sided auditory cortex.

Cluster #7: This is the last of the two-person clusters, and interestingly pairs our second "central auditory" individual (SHB, pRfR) with a pLfL subject, WB, reminiscent of Cluster #5, where another pLfL subject (SJ) is grouped with a "central auditory" client (MAB). While SHB's presenting complaint was with hearing speech in noisy situations, similar to MAB's self report, her dichotic-listening results were very different from his, characterized by a pattern of extremely high scores in the hypothetically preferred ears, and extremely low scores in the non-preferred ears (see Table II).

This pattern is theoretically the type one would see in a "split-brain"

individual, where normal interhemispheric communication is degraded to such an extent that the dichotic listening situation reduces to contralateral-only transmission from ear to cortex. Thus hemispheric specialization is highlighted over the normal case, due to the fact that cortical processing on the side preferred for a particular sound set receives no transcallosal interference (yielding very high scores for a sound set during attention to the preferred ear), while the nonpreferred side receives no transcallosal help (yielding very low scores for a sound set during attention to the nonpreferred ear).

This occasion points up the value of testing a subject with at least two sound sets designed to evoke opposite ear advantages, since, as Table II shows, the effect is shown in complementary directions, suggesting that processing on both sides is intact, and that the problem is limited to communication across the midline. This identification of a specific dysfunction in the context of functional savings thus provides an important insight into the nature of this subject's difficulty. Although the MRI films revealed an anatomically normal corpus callosum, other tests such as REPs/ABRs corroborated the hypothesis of a bilateral difficulty at the cortical level (see Appendix E for more detail).

One early conclusion regarding these data was that SHB's low delta coherence value (17%) was further evidence for breakdown in crosstalk between left and right auditory cortex in this subject. However, subsequent analysis of findings for all 15 Ss (see discussion under "Cross-modality" above) indicated that SHB's low delta coherence was in fact "appropriate" to her small periSylvian LHA. This conclusion led to a suspicion that a small periSylvian asymmetry (from 1% RHA to 6% LHA) is, in and of itself, a predisposition to pathology, perhaps consistently involving difficulties in interhemispheric communication. Reference to Figs. C3 and C4 above indicates that of the 7 subjects with a periSylvian HA in this range, all have indications of subtle neurological dysfunction:

JLM	mild learning disorder; mild dyslexia
JS	stuttering
SHB	central-auditory disorder
CJS	addicted smoker
AB	self-reported "sweets addict"
CB	addicted smoker
HR	addicted smoker

Connections between a relative lack of periSylvian asymmetry and pathological sequelae have been discussed by a number of authors (see Plante, op cit. for a summary, and new observations), and have clear implications involving abnormal hemispheric growth during prenatal development. In contrast, the results for the

other central-auditory case (MAB) "prove this rule" by presenting a very different pattern: a periSylvian LHA which is larger than 6%, combined with scores on other measures (see discussion under Cluster #1, and Appendix E) that clearly point to a disorder affecting the left hemiphere exclusively, with no indications of difficulties in interhemispheric transfer.

The other subject in this cluster has her own unusual features, presenting with the same "ipsilateral" pattern relating periSylvian HA (RHA) vs. ABR amplitude stability (REA) seen in another pLfL subject (SJ: see discussion for Cluster #5), which is opposite the "contralateral" relation between these two measures found, e.g., in both subjects (JL, CJS) of Cluster #3. In fact, by reversing the sign of only one of these two values for WB, her pattern of results would make her very similar to JL and CJS, an observation supported by the grouping produced by the cluster-analysis program at a subsequent level, putting all these subjects together as Cluster #9.

Cluster #8: That the cluster analysis at this point adds ES to the "strange bedfellows" group assembled via Clusters #1, 4, and 5 underscores earlier observations about ES (see p. 49 above), and may be related to her self-report of ambidexterity and the fact that WB (discussed under Cluster #7) is her daughter.

Clusters #9 and #10: The comparisons among these subjects have been addressed to some extent as they appeared in earlier clusters, and will not be further discussed here. However, it is tempting at this point to speculate how the three subjects with incomplete data would have been grouped, according to the patterns comprising these clusters.

PR: As shown in Fig. I7, top panel, PR's CNS profile very closely resembles that of JL, perhaps even more closely than did the profile of CJS's results which were grouped with JL's by the cluster analysis program (Cluster #3: cf. Fig. I3). The asterisk in Fig. I7 in place of PR's tone-pattern EA score marks the sole missing data point for this subject; the rest of his results compared with JL's might support the prediction that he would have a small behavioral REA for the tones.

The two primary points of departure from JL's data (qEEG resting asymmetry: LHA rather than JL's RHA; and ABR amplitude-stability EA: a smaller LEA than JL's) might be the result of this subject's use of cigarettes. The qEEG session and ABR test values represented in Fig. I7 were taken during a period while PR was smoking. As explained in the clinical study described in Appendix D, electrophysiological signs in PR distinguish him from his wife (HR), who is an addicted smoker, such that cigarette use has opposite effects in these two individuals, acting to increase the value of a measure in him while it decreases the same measure in her, etc. (for details, cf. Appendix D).

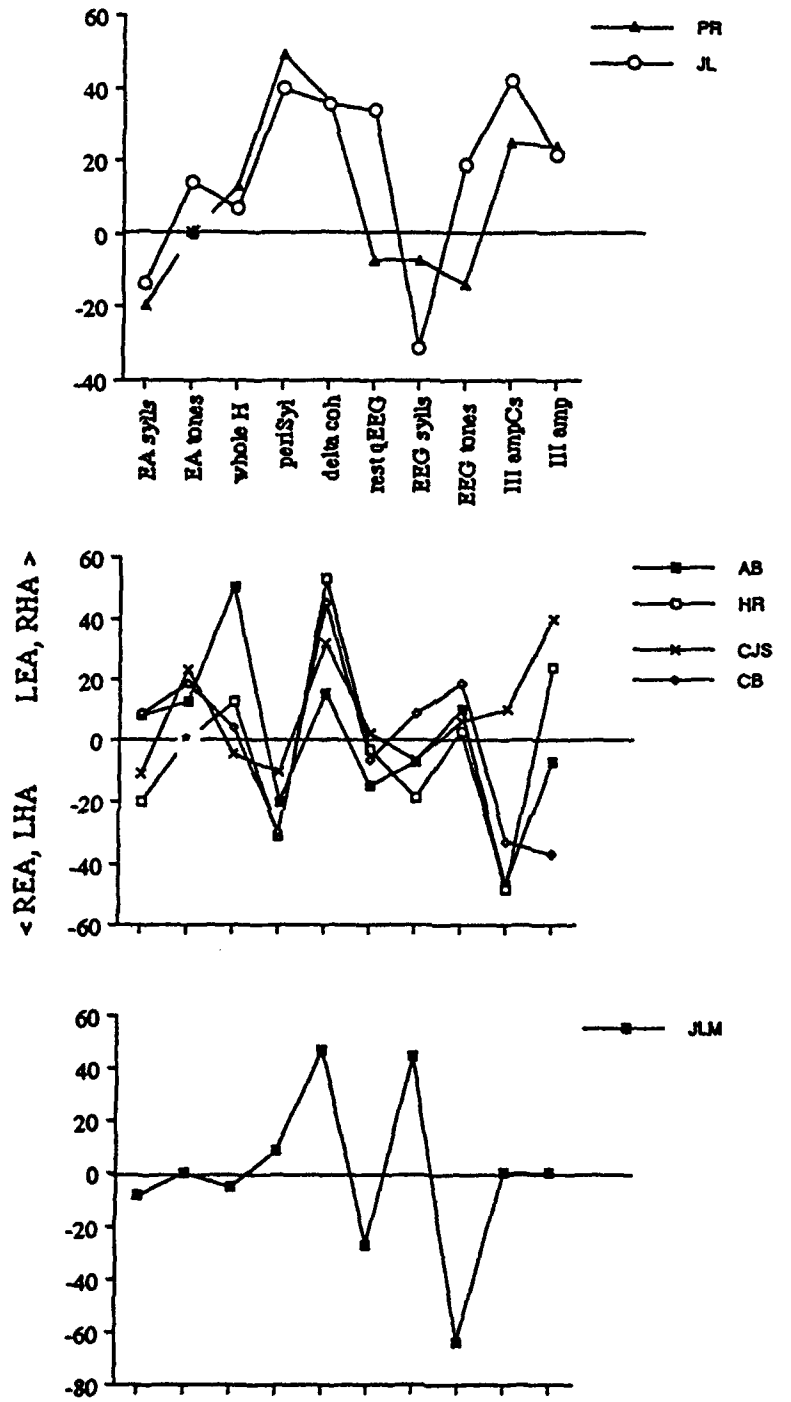


Figure I7. Hypothetical "clusters" combining each of the three subjects excluded from the cluster analysis for missing data, with one or another of the individuals or groups represented in Figs. I2-I6.

We have prior information about how qEEG resting asymmetry and ABR amplitude stability EA changed in HR going from a smoking to a non-smoking session: 1) her resting asymmetry shifted in a LHA direction, and 2) her ABR stability EA shifted in an REA direction. If PR consistently behaved opposite to her, this would predict that a re-test of PR during abstinence would result in: 1) his resting asymmetry shifting in a RHA direction, i.e., toward the value shown by JL in Fig. I7, and 2) his ABR stability EA shifting in a LEA direction, also toward JL's larger LEA.

The great similarity between the data of PR and JL provides evidence both supporting a conventional subject classification, since both are pRfR, and discounting one -- gender. As noted in the discussion of Cluster #1, 3, and 5 above, the patterns of responses observed in the subjects included in this Project to date suggest that there are categories of brain organization which may transcend gender.

HR: The point has been made above that the four subjects here with a history of substance abuse (specifically, 3 with addiction to cigarettes and 1 for sweets) have a number of characteristics in common. In fact, as illustrated in Fig. I7, middle panel, all four (including our smoker who was omitted from the cluster analysis due to missing data) have very similar CNS profiles. A visual comparison of these four profiles with the pair of PR and JL in the panel above suggests that CJS much more closely resembles HR and CB than she does JL -- as judged by the cluster analysis. Thus it is not surprising to find that the cluster analysis did in fact eventually group CB with the JL/CLS cluster (in Cluster #10 -- see Fig. I6, lower panel).

The commonality in these findings for the four subjects who share a history of addiction suggests an underlying neurological propensity for substance abuse, which is very much in keeping with current theory (cf. DeGood & Valle 1978, Sannita 1984, Cinciripini, 1986, Hasenfratz et al 1989). At least one of these subjects, HR, also has a history of hyperactivity, treated successfully with Ritalin (see Appendix D). Thus, also in line with current theory, the results for these individuals may in fact predict the form of a central-nervous system profile characterizing at least some hyperactive children. The connection between childhood hyperactivity (or some combination of the problems seen in the cluster of symptoms called Attention Deficit Disorder, and/or Attention Deficit with Hyperactivity Disorder, etc.) and adult substance abuse has been documented (Weiss & Hechtman 1986, Wender 1987), and it would clearly be of great value if such a battery as the one used here (or a subset of tests) could serve to identify children at risk for hyperactivity (and a subsequent history of substance abuse as adults) even before symptoms appear.

If such an "early identification" strategy were made available, it is possible that "early intervention" techniques might be developed that could relieve these individuals of their terrible personal burden, and society of the social, political, and overwhelming economic burdens which such individuals represent. Identification of the neurological signs which these three subjects have in common may be one demonstration of the power of the CNS Project's coordinated approach, which in this case may have taken the first step toward definition of very specific indices for a subtle neurological deficit no less real for its subtlety, though perhaps because of it, invisible to conventional types of testing. Such objective documentation of the "difference" between "self-medicating" substance use vs. other types could serve not only to reassure such individuals that their problem "is in their brains, not in their minds," but might more importantly lead to new ideas for therapeutic design and assessment.

JLM: The fact that JLM's data set is missing 3 of the 10 possible scores does not resolve her extreme differences from the other subjects, which are still dramatically apparent in the 7 scores that are available for her. Thus at least in the interim she should probably be considered unique among the individuals tested here (Fig. I7, bottom panel).

Reading the measures from left to right, she appears very similar to the three "addicted" individuals in the middle panel above her, according to the pattern of the first 5 scores: a moderate REA for syllables, (cf. CJS and HR), a <6% periSylvian LHA (cf. CJS, AB, and CB), a small whole-hemisphere RHA (cf. CB), a high delta coherence (cf. all four of the above), and a clear LHA in resting qEEG (cf. CB, AB, and HR). However, the next two scores set her apart from all the other subjects: a large qEEG RHA for the syllables, and an equally large qEEG LHA for the tone patterns. The only possible clue to the source of this unusual pattern is the fact that, also unique among these subjects, she has a <1% periSylvian RHA paired with high T3/4 delta coherence (47.2%: cf. Fig. C3). The only other subject with a < 1% periSylvian RHA was JS, with a history of stuttering, and his delta coherence was low (19.4%).

Our earlier conclusion (cf. Fig. C4) that only the periSylvian/coherence pattern shown by JS was abnormal might have been too conservative. Perhaps, as suggested in the discussion of Cluster # 7 above, it would be more accurate to identify any virtually symmetrical periSylvian configuration (between 1% RHA and 6% LHA) as predictive of "unusual" performance on tasks involving complex auditory perception, such as dichotic listening (cf. the work on Specific Language-Impaired children by Plante, op cit.).

V. Summary of findings.

The general findings of this series of experiments may be summarized as follows:

1. Each individual can be described in terms of a "sidedness bias" expressed as the pattern of results on the various tests comprising each subject's "individual CNS profile."

2. Within subjects, the "individual CNS profiles" tends to reflect "internal consistency." Background knowledge of the subjects suggests that in some cases, departures from such consistency may be interpreted as signs of subtle dysfunction below the threshold of clinical definitions of neuropathology, such as mild stuttering, mild learning disorder, central auditory dysfunction, or a history of hyperactivity and/or substance abuse. For some individuals, the inconsistencies in the asymmetry patterns provided highly specific predictions regarding the nature of the difficulty.

3. In the 15 individuals tested here, the individual profiles could be clustered as sets of "group CNS profiles." These group profiles seemed to be independent of gender and handedness categories, yet were consistent with other types of shared subject characteristics such as the dysfunctions noted above. This observation not only suggests a richer variety of brain organization related to asymmetries than suspected, but also supports the possibility of a quantitative basis for categorizing individuals with regard to asymmetrical organization. Such a classification could prove invaluable for use in a wide range of issues in human behavior, from describing personality characteristics and learning styles, to identifying predisposition for certain types of disorders. .

4. While in some subjects, the individual patterns of "internal consistency" were clearly related to the behaviorally-measured patterns of asymmetries, this was not the case in all instances. Findings from this first set of 15 individuals support the expectation that more data on the distribution of the dependent variables included will lead to further insights into the specific ways in which they underly behavioral measures of performance such as ear advantages.

5. Possibly crucial to this last point is the observation under three separate techniques of a "persistence effect" in the brain, in which changes induced during activation conditions may persist for as long as 30 minutes following the particular activation. It is possible that there are distinct individual differences in the time course of such an effect, and that the apparent inconsistencies between internal asymmetries and behavioral performance may be in part accounted for by individual differences in the rapidity with which the CNS "returns to baseline" following activation.

With regard both to these, and to the more specific points made in the course of the analysis, it should be understood that all conclusions of Phase One of this Project are of necessity exceedingly preliminary, given the small number, and variety, of subjects tested. All summary statements should be qualified as being based only on these particular 11 female and 4 male subjects, tested on these particular 10 variables.

However, the individual findings as cited and discussed below are sufficiently discrete as to serve as specific, testable hypotheses with predictive value, for a variety of normal as well as disordered populations.

1. The central auditory nervous system of each individual has a "sidedness bias" which can be specifically quantified in terms of an individually unique "resting CNS profile." The bias is expressed both anatomically and physiologically, from brainstem to cortex.

An individual's "resting CNS profile" can be articulated in terms of dependent variables available from several noninvasive methods. The particular sidedness-bias CNS profiles described in this report comprise: brainstem amplitude ear advantage (EA), brainstem amplitude-stability EA, whole-hemisphere anatomical hemisphere advantage (HA), periSylvian anatomical HA, resting qEEG HA (beta power asymmetry over auditory-cortex electrode locations T3/4), and resting qEEG delta coherence over T3/4.

These features were selected to highlight asymmetrical organization within the auditory CNS, and a different set may be required for studying other aspects of the human CNS, such as organization in other sensory systems, motor control, or cognitive performance. However, it is possible that due to the basic nature of the measures used here, they would also prove useful as aids in interpreting individual characteristics regarding a variety of topics relating human brain and behavior. Future researchers may find that meaningful interpretation of almost any type of human behavior is extremely difficult in the absence of information regarding the "sidedness bias" of each individual CNS.

2. While each individual's "resting CNS profile" is composed of a set of values unique to that subject, overall profile shapes may more generally express a finite "repertoire" of relevant brain organization.

As more is known about the distribution of these measures, it may be possible to predict a variety of individual characteristics (e.g., performance on selected tasks,

presence of subtle neurological disorder) based only on the nature of the individual "resting profile." The profiles may also be useful as a means of "bottom-up" empirical grouping of subjects which could address current difficulties with a priori grouping based on inadequate individually-specific information.

3. The CNS profile for each individual tends to be "internally consistent."

Thus a system which favors the left ear peripherally (in brainstem amplitude EA and/or amplitude stability EA) will favor the right auditory cortex centrally (in terms of periSylvian HA, and in terms of either resting qEEG beta HA and/or level of resting qEEG delta coherence over T3/4). Departures from consistency may be diagnostic of neurological dysfunction, even in individuals who are neurologically normal by conventional criteria.

4. There is no form of either a "resting CNS profile" or a total CNS profile (i.e., combining resting values with those measured during activation protocols -- for a total of 10 variables measured for this report) which covaries with subject handedness characteristics.

Subject groupings based on test results alone seem to cut across conventional "external" sidedness categories such as personal handedness and familial handedness (including family history of the occurrence of twins), at least for the 15 subjects tested here. However, results on some tests are suggestive (e.g., all the personal-left / family-left individuals have virtually no brainstem amplitude EA, and very low delta coherence over auditory cortex). As more representatives of these and other sidedness groups are tested, such "CNS profiles" may serve to validate the conventional categories, and/or articulate new ones, with promise for new insights into the relative saliency of these types of measures for predicting behavior.

5. There is no form of "CNS profile" which covaries with subject gender.

Due to the small number of men included in this study, such a conclusion is extremely preliminary. However, for this group of individuals, the profiles do not group males with males, but indicate that each of these males is more like members of one or another of the female CNS-profile groups than they are like each other.

6. There is no single factor or pair of factors which can alone predict the patterns of ear advantages in any given subject (whether "split," "two LEAs," "two REAs," or any reversed pattern).

The degree of "internal consistency" (i.e., among the variety of anatomical and physiological asymmetries measured) was much greater in these subjects than was the obviousness of a simple relation between internal CNS design and the behaviorally-measured asymmetries. For some subjects, the connection is completely straightforward: i.e., the sound sets evoke "split" qEEG hemisphere advantages very similar to the "split" patterns of behaviorally-measured ear advantages; for others, a combination of features may be necessary to account for deviations from this simple rule.

7. The direction and magnitude of the periSylvian asymmetry may be used to predict the value of the qEEG delta-band coherence recorded over auditory cortex at electrode locations T3 and T4.

In the subjects tested here, this prediction operates according to the following rule: 1) if the periSylvian asymmetry favors the right hemisphere (RHA), the resting qEEG delta coherence over T3/4 will be 28% or higher; 2) if the periSylvian asymmetry is LHA, the resting coherence will be lower than 28%. Individuals in which the relation between delta coherence and periSylvian HA depart from the rule may either be left-handed women from left-handed-female families, or may suffer from neurological deficits expressed as stuttering (primarily in men?) or substance addiction (primarily in women?).

8. Individuals with a small periSylvian hemisphere advantage (HA), ranging from 1% RHA to 6% LHA, will be predisposed to a variety of problems.

The types of difficulties observed in this report include: 1) mild learning disorder including mild dyslexia, 2) stuttering, 3) central auditory dysfunction, and 4) hyperactivity/ substance addiction. Plante and colleagues (see references) have also observed small periSylvian HAs in specifically-language-impaired individuals and their families.

9. Individuals who are addicted to substances as adults, and/or have a history of hyperactivity during childhood, will have a recognizable "CNS profile," with covarying components indicative of underlying neuropathology.

If such a subject is studied during a time when she/he is using the substance of choice, this profile will include T3/4 delta coherence higher than predicted by the rules stated in #7 above.

[In a series of related clinical studies conducted with other support, we have additionally found that, if these individuals are tested during abstinence from their substance of choice, the T3/4 delta coherence may be reduced to a "normal" level, i.e., predicted by their periSylvian HA.

During abstinence, they may also have a subcortical "release sign" consisting of hyperstability in the auditory brainstem response (ABR), which we have termed the "smoker's needle" (although it has been observed in individuals reporting a history of use of a variety of substances, not just cigarettes). A simple "stress test" consisting of repeated testing may act to bring this abstinence hyperstability within a normal range, mimicking the effect of the substance to which the individual is addicted.

The "smoker's needle" in the brainstem response co-varies with T3/4 delta coherence in the following way: 1) if the subject is tested during a period of substance use, the brainstem response will show normal levels of stability, and T3/4 delta coherence will be higher than predicted on the basis of periSylvian asymmetry (see #7 above); 2) if tested during a period of abstinence, the "smoker's needle" brainstem hyperstability will be present, accompanied by a decrease in T3/4 delta coherence to a "normal" level, i.e., to a level predicted on the basis of the periSylvian HA.

This combination of equal but opposite electrophysiological effects monitored at two levels of the CNS, points to the brainstem as the location of the underlying pathology, and suggests that at least some addicted individuals are "self-medicating," employing a particular substance which acts to increase cortical coherence to abnormally high levels in order to bring brainstem stability down to within normal limits.]

10. The "CNS profiles" of Oriental vs. Western brains may be distinctive.

There is a large literature, and much folk wisdom, regarding the distinctions between Oriental and Western brains. The findings of this study concur, in that CNS profiles of two individuals from gene pools with Oriental contributions are very similar to those describing two Western women who are both left-handed from families including other left-handed women.

11. Associated with all the auditory-activation conditions observed here, as well as in simple motor tasks such as hand flexion, there are "residual effects" which may persist in the brain for as long as 30 minutes following the original test condition.

It is possible that these "macroneurophysiological" effects are related to "microneurophysiological" phenomena such as "long-term depression" (LTD) and "long-term potentiation" (LTP) which are currently topics of interest in the study of single-cell neurophysiology. Certainly the present results show evidence of persisting activity which is clearly related to preceding test conditions, whether quantified using qEEG, PET, and MRS (not reported here), and preliminary indications are that the time course of the phenomenon is similar under all these techniques, in spite of the differences in the index of physiological response represented by each.

The persistence is best observed by using a design of spaced resting conditions, such that measures taken during an initial baseline resting condition may be compared with similar measures during succeeding activation and rest conditions. The effect may take the form of "reduced" versions of changes induced during preceding activation, e.g., a resting condition tested immediately following an activation condition involving left-ear attention to syllables may show a reduced "echo" of the right-hemisphere advantage (RHA) evoked during the actual task. Or, the persistence effect may be expressed as a form of "overshoot," such that the RHA during resting condition B will be larger than the one occurring during the actual activation condition A.

The salience of these effects emphasizes the importance of experimental design using noninvasive "macroneurophysiological" methods, including mitigating against the validity of the common practice of successively subtracting a temporal chain of activation conditions under the dual assumptions that: 1) there are no such persistence effects, and 2) an untrained individual's brain responds exactly the same way during every successive presentation of the same (or hierarchically nested) test conditions.

It may be that this persistence effect represents the first new basic type of behavior-related neurophysiological phenomenon observed with the new noninvasive methods. If so, it would serve to illustrate the dramatically different view of the brain provided by the new noninvasive methods and their levels of resolution, and supports the idea that techniques working at these levels of resolution may be much more relevant to the relation between brain and behavior than are the methods and resolution of single-unit physiology. Certainly such an

effect would have essential implications for many aspects of human neuroscience, from experimental design involving the simplest activation protocols, to study of changes in the time course of the persistence effect as a function of variables such as: 1) stimulus characteristics (intensity, activation breadth), 2) task difficulty, and 3) brain pathology.

VI. Conclusion and implications

The goal of understanding the ways in which brain structure and function underlie human behavior is an ambitious -- and long-frustrated -- one. During the first century of neuroscience, students of the human brain were forced to depend either on extrapolations of results from highly invasive techniques in non-human animals, or on human-test methods limited essentially to the "whole organism response." Necessarily such constraints led researchers to focus on describing the features of populations rather than individuals, though both lay and professional wisdom recognized the overwhelming salience of individual characteristics.

Now, over the last decade, researchers have acquired an array of noninvasive tools which provide the temporal and spatial resolution requisite for sophisticated study of living, healthy as well as disordered, brains. From the point of view of the old methods, the increase in sensitivity to individual characteristics of brain structure, physiology, and function embodied in these new techniques is almost daunting, and has led some researchers to subsume the new levels of sensitivity in statistical methods designed for the old levels of access. Even preliminary studies, however, such as the current report, indicate that there is virtually everything to be known about the rich and various "repertoire" of ways in which brain organization is differentially expressed in behavior from individual to individual.

Although the concepts articulated earlier regarding the crucial importance of individual characteristics may not seem like unusual concepts, the focus on a "bottom-up" rather than a "top-down" approach such as the one employed here, for studying and classifying human behavior is one that has not received much attention. The surprising lack of interest in individuals which is endemic throughout almost all sciences concerned with human behavior may be analyzed as having its root in two causes.

First, the level of specificity characterizing most tests for studying the human CNS has, until the past 5-10 years, been so crude that the dramatic range of normal variation and even more dramatic, of the "repertoire" of the expressions of brain pathology, have not been appreciated. For example, until the past five years, there was no way to quantify such a measure as "periSylvian asymmetry" in the living brain, and classifications of subjects related to brain asymmetry were forced to depend on such vague measures as which hand was used for writing.

Second, until the advent of personal computers (also occurring within the last 10 years), data-processing capabilities sufficient to handle anything other than group data were not generally available. Thus interest in individual differences,

necessarily dependent on the use of within-subject nested repeated-measures designs, has been at best, discouraged. Indeed, the most commonly used statistical tests were originally designed under the assumed constraint that the calculations were to be done by hand, and it is clear that this assumption alone would insure that the emphasis would be on "population statistics."

It is not surprising therefore that the focus of studies of human behavior and its neuroanatomical and neurophysiological correlates has been limited almost exclusively to observations in a priori-defined groups, and that a typical experiment in "neuropsychology" or "cognitive neuroscience" consists, e.g., of comparing the performance of 25 subjects from group A vs. 25 subjects from group B on a single test, and analyzing results in terms of a statistical test which relegates differences between individuals to the "error term." Thus a common complaint in this research is the lack of replicability and the inconsistency in such group data --not surprising given the almost certain lack of homogeneity in groups defined in the usual way, i.e., according to one or two measures such as gender and handedness.

Even more disappointing than these experimental outcomes has been the way in which they have been received, namely, by dismissing the test (e.g., on the grounds that it could not show that the two groups were significantly different) rather than by challenging the assumptions of the approach. In fact, it is possible that many tests which have been thus vilified "failed" in this way because they were in fact more sensitive to individual characteristics -- and thus more powerful as tools for studying behavior -- than their users, seeking corroboration of the assumed "population characteristics" suspected.

This is of course an old problem, which may be characterized as the "dirty diamonds" approach to scientific method: "if a test [the hoped-for diamond] does not give the expected results [does not support the a priori group definitions -- therefore, is 'dirty'], abandon the test on the grounds that it yields inconsistent results [throw it away]." Perhaps a little wishful rubbing of those "inconsistent" results would reveal the varieties of consistencies that lie beneath the surface of the enforced group definitions, representing facets of the individuals, waiting to be revealed.

Although this is an old problem, it is one which continues to present obstacles to understanding human behavior. Its implications range from annoying to serious, with the potential of retarding or even misdirecting research, sometimes with costly consequences, in time, money, and misinformation. One small example is provided by the test method called dichotic listening. This research, while not expensive on a test-by-test basis, has been pursued by hundreds of workers over more than three decades on thousands of subjects, yielding

countless presentations and publications.

Most of this work emphasizes group data, and from the beginning, researchers have complained about the inconsistency of results, even at times declaring that the effect of an "ear advantage" was an ephemeral artifact due to novelty, which was thus notoriously nonreplicable and which would go away with training. Attention to individual differences has revealed not only that ear advantages are robust and replicable, and if anything increase in saliency with training (Lauter 1982), but that by examining the individual data beneath the group averages, one can derive new and entirely unsuspected information from old data (Lauter 1983).

The emphasis on population statistics further impedes progress in understanding human brain and behavior as its assumptions and procedures continue to dominate research with other, more expensive tests. The incredible advances in sensitivity to individual characteristics which are offered by methods such as evoked potentials, quantitative EEG, MEG, and PET are for the most part being ignored, if not overtly rejected, by researchers who were trained in the old methods which perforce considered individual characteristics only as a source of error. Although this is psychologically understandable, scientifically it is tantamount to using an electron microscope only to look at objects at the level of resolution provided by light microscopes -- using new techniques to answer questions formulated under the constraints of old techniques.

One example of a decision of this sort is the one by which researchers have chosen to ignore the dramatic individual differences in waveform morphology of evoked potentials, and the associated differences in peak stability. With minor modifications of standard collection and analysis techniques, we have shown that a simple measure of waveform stability provides a dramatic increase in sensitivity to a wide variety of characteristics, from ear differences to unsuspected neurological deficits (see Appendices D and E).

The refusal to "look through the microscope" may take more dramatic forms when financial resources are available sufficient to design entirely new analytical techniques, such as those currently in vogue for processing the results of PET activation studies. Proponents of these techniques have themselves articulated that a prime motivation is the frustration felt when a given subject does not show the expected response, or when an individual's response changes under retest. The resolution of this frustration has been to take a literally procrustean approach, stretching and shrinking brain images from individuals to fit a standard, and then averaging over subjects to generate an image of the "group brain."

Thus this research using a revolutionary noninvasive technique which provides pictures of individual living human brains with a temporal resolution of 40 sec and spatial resolution of 5 mm is driven by a priori assumptions based essentially

on century-old "bedside techniques" of clinical neurologists and psychologists. Those techniques, often supremely sophisticated given the limitations of access, perforce were constrained to assessing the "whole organism response," and thus realistically proceeded on the assumption that individuals are more alike than they are different, and that they respond mechanically the same trial after trial.

It takes only one PET experiment --or a study with any other of the new noninvasive techniques -- to demonstrate the simple falsity of these assumptions. In fact, the sensitivity of these new devices provides a basis for a new and opposite assumption: that a more appropriate null hypothesis for human neuroscience is that every individual brain is different (even that the two sides of every brain are different). This places the burden for the research on finding the ways in which those differences can be comprehended into a "repertoire" of modes by which brain structure and function are related to behavior.

Certainly this methodological and philosophical situation is a temporally local one in the history of neuroscience, a predictable result of the suddenness with which the new monitoring devices have become available. The study of the human brain has, over the course of a single decade, been presented with tools which increase access to living healthy brains manyfold. The leap in orders of magnitude of resolution (cf. Figs. i1 and i2) has naturally created a lag between the expectations of researchers trained in the use of the old techniques, and the capabilities offered by the new tools. It is to be expected that as we become skilled in using the new tools to their full capacity, learning from them instead of forcing new data into old molds, our concepts about how the human brain works and how it goes wrong will undergo radical changes.

Thus it may be said that, for the endeavor of "human neuroscience," it is 1850 all over again. As we learn to appreciate the power of the new devices, and to interpret the increasing levels of detail which they make available, we may come to recognize in this "Decade of the Brain" that we are on the threshold of the "Century of the Human Brain," with its promise of new and unsuspected insights into the varieties of function and dysfunction in the human CNS.

References

Berlin, C. I., L. J. Hood, P. Allen. (1984). Asymmetries in evoked potentials. In C.I. Berlin (Ed.), Hearing science; recent advances. San Diego, College-Hill Press, pp. 461-477.

Cinciripini, P. M. (1986). "The effects of smoking on electrocortical arousal in coronary prone (Type A) and non-coronary prone (Type B) subjects." Psychopharmacology **90**: 522-527.

DeGood, D. E. and R. S. Valle (1978). "Self-reported alcohol and nicotine use and the ability to control occipital EEG in a biofeedback situation." Addictive Behaviors **3**: 13-18.

Hasenfratz, M., C. Michel, R. Nil, K. Battig. (1989). "Can smoking increase attention in rapid information processing during noise? Electrocortical, physiological and behavioral effects." Psychopharmacology **98**: 75-80.

Heidbreder, A. and J. L. Lauter (1983). "In-the-ear sound-delivery system for use in positron emission tomography." Central Institute for the Deaf Periodic Progress Report **25**: 31-32.

Lauter, J. L. (1982). "Dichotic identification of complex sounds: Absolute and relative ear advantages." Journal of the Acoustical Society of America **71**: 701-707.

Lauter, J. L. (1983). "Stimulus characteristics and relative ear advantages: A new look at old data." Journal of the Acoustical Society of America **74**: 1-17.

Lauter, J. L. (1984). "Contralateral interference and ear advantages for identification of three-element patterns." Brain and Cognition **3**: 259-280.

Lauter, J. L. (In Press). "Processing asymmetries for complex sounds: Comparisons between behavioral ear advantages and electrophysiological asymmetries based on quantitative electroencephalography (qEEG)." Brain and Cognition .

Lauter, J. L., P. Herscovitch, C. Formby, M. E. Raichle. (1985). "Tonotopic organization in human auditory cortex revealed by positron emission tomography." Hearing Research **20**: 199-205.

Lauter, J. L., P. Herscovitch, M. E. Raichle. (1988). Human auditory physiology studied with positron emission tomography. In J. Syka and R. B. Masterton (Eds.), Auditory pathway. New York, Plenum, pp. 313-317.

Lauter, J. L. and R. L. Loomis (1986). "Individual differences in auditory electric responses: Comparisons of between-subject and within-subject variability. I. Absolute latencies of brainstem vertex-positive peaks." Scandinavian Audiology **15**: 167-172.

Lauter, J. L. and R. L. Loomis (1988). "Individual differences in auditory electric responses: Comparisons of between-subject and within-subject variability. II. Amplitudes of brainstem vertex-positive peaks." Scandinavian Audiology **17**: 87-92.

Lauter, J. L., F. Tucker, K. Hubner. (1990). "Quantitative demonstration using positron emission tomography, of regional activation, response asymmetries, and residual effects of hand flexion in the normal human brain." In-house report, University of Tennessee Medical Center at Knoxville.

Levine, R. B. and P. M. McGaffigan (1983). "Right-left asymmetries in the human brain stem: auditory evoked potentials." Electroencephalography and Clinical Neurophysiology **55**: 532-541.

Plante, E. (1991). "MRI findings in the parents and siblings of Specifially Language-Impaired boys." Brain and Language **41**: 67-80.

Plante, E., L. Swisher, R. Vance. (1989). "Anatomical correlates of normal and impaired language in a set of dizygotic twins." Brain and Language **37**: 643-655.

Plante, E., L. Swisher, R. Vance, S. Rapcsak. (1991). "MRI findings in boys with Specific Language Impairment." Brain and Language **41**: 52-66.

Plante, E. and L. Turkstra (1991). "Sources of error in the quantitative analysis of MRI scans." Magnetic Resonance Imaging **9**: 589-595.

Sannita, W. G. (1984). "Electrophysiological concomitants of the long-term withdrawal from cigarette smoking: A pilot study." Research Communications in Psychology, Psychiatry and Behavior 9: 273-283.

Sergent, J. (1983). "Role of the input in visual hemispheric asymmetries." Psychological Bulletin 93: 481-512.

Weiss, G. and L. T. Hechtman (1986). Hyperactive children grown up: Empirical findings and theoretical considerations. New York, Guilford.

Wender, P. (1987). The hyperactive child, adolescent, and adult. New York, Oxford Press.